VOLUME VI (Old Series, Vol. XI) JULY, 1932 NUMBER 1

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

CONTENTS

Issued Monthly

Ann Arbor, Michigan

The Rôle of Specific Carbohydrates in Pneumococcus Infection and Immunity*†

By Oswald T. Avery, M.D., *New York City*

MR. President; Fellows of the American College of Physicians:

I count it a great privilege to be able on this occasion to express personally my deep sense of appreciation of the distinguished honor conferred upon me by the American College of Physicians. In awarding me the John Phillips Memorial Prize I feel that you have been far too generous in your appraisal of my share in the work for which this distinction is granted. I am conscious that whatever merit may accrue to the studies in which it has been my privilege to participate is due in great part to the happy auspices under which the work is carried on, and in large measure to the devoted and hearty cooperation of my associates. To them, I am indebted for an association that to me has been a source of genuine pleasure and great helpfulness; and to them I am happy on this occasion to acknowledge my obligation.

I find great satisfaction in the thought that in making this award, you are symbolizing in a far larger sense than the mere personal recognition implies, your faith in the spirit of research and the principles of practice expressed by Osler in these words: "To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions. To carefully observe the phenomena of life in all its phases normal and perverted, to make perfect the most difficult of all the arts, the art of observation, to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false —these are our methods. To prevent disease, to relieve suffering and to heal the sick—this is our work."

To all who cherish these ambitions, cultivate these methods, and delight in this work, the example of him in whose memory this award has been established will remain a continuing source of inspiration.

Permit me once more to assure you

---

*From the Hospital of the Rockefeller Institute, New York City.

†Delivered at the San Francisco Meeting of the American College of Physicians, April 6, 1932, at the presentation of the John Phillips Memorial Prize.

of my grateful appreciation of the signal honor of being enrolled as one of the recipients of the John Phillips Memorial Prize.

AN important advance in the study of infectious diseases came with the knowledge that bacteria, though simple in form and structure, exhibit differences in biological specificity as sharply defined as are those characteristic of the more complex forms of life. The study of the immunological specificity of microorganisms is not only necessary in the elucidation of the biological relationships existing between varieties of the same species of bacterium but is essential to the working out of epidemiological problems and to the development of methods useful in the control of infectious diseases by specific therapeutic and prophylactic measures.

Leaving out of consideration the promising but difficult field of chemotherapy, the problems of specific cure and prevention of infection lie in the attempt to interpret and imitate by artificial procedures certain protective processes of nature which constitute that which we call immunity. In order to imitate successfully the natural processes involved in spontaneous recovery from disease, it is necessary to know the nature of the specific reactions between the infecting agent and the body tissues of the host. The specificity of these biological processes is advantageously studied by means of the so-called immunity reactions. These serve as a measure of the capacity of the animal organism to produce protective substances, and they afford a means of studying the interaction between these specific antibodies and the infectious microorganism when both are brought together in the animal body or in the test tube.

Investigations on the specificity of these reactions have added much to our knowledge of the many and diverse problems of infection. The study, however, is one of varying complexity; the methods suitable in one instance fail utterly when applied to another type of infection. While the mechanism of the interaction between host and parasite has to a certain extent been exposed through the brilliant discoveries of Metchnikoff, Ehrlich, Behring, Bordet and others, the immediate problem lies in reconstructing for each microbe a more precise knowledge of the biological properties peculiar to it and the specific reactions which the body develops against it. One approach to this problem is the attempt to relate specific differences in biological behavior to fundamental differences in the function and chemical composition of the component parts of the bacterial cell and to determine the character of the tissue responses to these separate constituents. The total immune response of the host comprises not alone a reaction to the parasite as a whole, but, in addition, the specific and individualized responses to the chemically distinct and immunologically specific bacterial constituents.

For the past several years under the direction of Dr. Rufus Cole a number of us on the staff of the Hospital of the Rockefeller Institute have been seeking to acquire a more intimate knowledge of the relation between the immuno-chemistry and the biological activities of pneumococcus, the most

frequent and one of the most fatal of the microbic incitants of pneumonia in man.

On this occasion I shall review briefly one phase of the studies, namely, the rôle of specific carbohydrates in pneumococcus infection and immunity. Because of the limited time at my disposal, I shall of necessity be obliged to omit reference to the valuable contributions of that large group of other investigators who, both in this country and abroad, have added so much to our knowledge of the problems of pneumococcus pneumonia.

You are already familiar with the renewed impetus that was given to the study of pneumonia by the working out of the biological classification of pneumococci which made possible the recognition of sharply defined and specific types within this previously confused species of microorganisms. You will recall that by the application of this method it has been possible to determine the frequency of occurrence of these specific types in pneumonia, and to recognize differences in the severity and mortality of the infections they produce; that a study of the presence of pneumococci in the mouth secretion of healthy individuals proved the dissemination of the disease-producing types by healthy carriers and convalescents and suggested a new interpretation of the epidemiology of the disease; and finally that the knowledge of type-specificity among pneumococci provides the only rational basis for the possible development of specific therapy by immune serum, which in the treatment of type I infections, at least, has proved of distinct value.

Pneumococcus is a unicellular microorganism which under well-defined conditions of growth is surrounded by an envelope of material known as the cell capsule. This capsular layer is particularly well developed in the case of pneumococci capable of growing and multiplying in the animal body. During growth these encapsulated cells elaborate in the medium of their environment a diffusible substance which in soluble form retains the type-specificity of the bacterial cells from which it is derived. This soluble specific substance is found not only in the filtrates of young cultures but also in the body fluids of animals experimentally infected, and in the blood and urine of patients during the course of pneumococcus pneumonia. The function of elaborating this specific material is most highly developed in the most virulent organisms. There are grounds for the belief that the capsule of these virulent cells is composed largely of this soluble specific substance. Thus, there is disposed peripherally about the cell an outer layer of capsular substance which reacts specifically with the serum of immune animals. The reaction is remarkably specific, occurring only when the antiserum and the reacting substance are both of the same specific type. These immunological reactions form the basis of the original classification and were worked out before there was any knowledge of the chemical nature of the substances upon which type-specificity depends. The actual isolation of these specific substances in purified form, the determination of their chemical constitution and their relationship to the immunological properties of the

cell as a whole are problems to which I shall direct attention.

The type-specific capsular substances of pneumococcus, first chemically isolated by Dr. Heidelberger, have been found in each instance to belong to the class of sugar-like substances, namely, the carbohydrates. No matter from what type of pneumococcus these specific substances are recovered they all possess in common the chemical properties of complex sugars—the polysaccharides. But, interestingly enough, the capsular polysaccharide derived from each specific type of organism is chemically distinct, each possessing unique chemical properties which serve to differentiate it sharply from the others. Moreover, solutions of these capsular polysaccharides in chemically purified form, exhibit immunologically the same specificity as do the bacteria of which they originally formed a part. Some idea of how remarkably reactive these sugars are may be judged from the fact that, by the use of an appropriate serum, their presence may be detected in dilutions as high as 1:5,000,000.

Dr. Heidelberger and Dr. Goebel, studying the chemistry of the capsular polysaccharides, have shown that these substances are unusual compounds of simple sugars and uronic acids. Although possessing many properties in common, they exhibit characteristic differences in the degree to which they rotate the plane of polarized light and in their acid equivalent number. For example, of the specific substances of the first three types of pneumococcus, the type I polysaccharide differs sharply from the other two in containing nitrogen as an integral part of the molecule, and in possessing basic as well as acidic properties; on the other hand the type II polysaccharide is a dextrorotatory weak acid and the type III a levorotatory strong acid, neither of which contains any nitrogen in the molecule. The fact that the particular constituent determining type-specificity is chemically a carbohydrate is the more striking since immunity reactions have hitherto been considered exclusively the function of proteins. Of equal importance is the fact that this selective specificity is in each instance determined by the chemical constitution of the particular polysaccharide in the capsule and that the presence of this morphological structure conditions both the invasiveness of the parasite and the immune response of the host.

The fact that polysaccharides elaborated by bacteria growing in the focus of disease may be found in the blood and urine, unchanged in specificity, indicates that the body possesses no enzymes capable of breaking them down into simpler sugars. There is no evidence that these complex bacterial sugars *as such* are directly responsible for the intoxication accompanying the infection. So far as known they are not primarily toxic, at least not in the sense of true bacterial toxins. There are facts, however, which indicate that indirectly at least they may have a harmful effect upon the natural processes of recovery. Because of their specific capacity to bind antibodies, they tend to neutralize the immune substances in the blood and thus prevent the protective antibodies from reaching the infected areas. Moreover, the capsular polysaccharides are known to exert an inhibiting action on phagocytosis, one

of the most important cellular defenses of the body against pneumococcus infection.

Theoretically, at least, there is no apparent reason why these complex sugars as isolated substances should not by themselves be capable of stimulating the formation of antibodies in the animal body. Assuming that they are of sufficient molecular size, they possess in complexity of structure and colloidal behavior certain properties generally considered essential to the antigenicity of proteins. Indeed, Francis and Tillet have found that in the present state of purity the capsular polysaccharides are capable of inciting antibody production when injected in minute amounts into the skin of convalescents and normal individuals. However, with few exceptions all attempts to evoke any immune response in animals with the highly purified polysaccharides alone have been uniformly unsuccessful. On the other hand, the more these carbohydrates are chemically purified, the more reactive they become in the specific serum of immune animals. Under these conditions it appears that, removed from the bacterial cells, the capsular polysaccharides still retain unimpaired the property of binding with antibodies, although in this form they become quantitatively less active in stimulating antibody production in animals. In this respect they may rightly be included in the group of immunologically important substances which Landsteiner has called haptens,—substances which have lost more or less completely their antibody-stimulating function without impairment of the property of specifically combining with antibodies.

The elaboration of the capsular polysaccharide is an important function of the cell. When this function is suppressed or inhibited, as it may be under certain experimental conditions of growth, the capsule is no longer formed. As a result the organisms lose their type-specificity and exhibit only the common, undifferentiated characters of the species. On the basis of colony differentiation these degraded organisms are spoken of as the "R" or rough forms, and the original encapsulated types are referred to as the smooth or "S" organisms. The unencapsulated R forms of pneumococci, irrespective of their type derivation, are no longer capable of invading the animal body; they have lost their virulence, and are readily taken up and destroyed by the phagocytes of the host; immunologically they exhibit only the species-specificity common to all the degraded R forms of pneumococcus. This transformation resulting in a loss of specific characters may occur in the animal body as well as in the test tube. However, these degraded, avirulent variants do not necessarily remain the harmless saprophytes they were originally thought to be, since it is now known that under suitable conditions they may regain all the specific characteristics that distinguished the original parasitic type from which they came.

Of even greater biological interest is the phenomenon of the inter-convertibility of the specific types of pneumococcus. Griffith of London first showed experimentally by a special technic in mice that R forms derived from one specific type of pneumococcus may be caused to acquire the characteristics of

another specific type. This important fact has been confirmed by a number of investigators. In addition, Dawson and Sia by special cultural methods, have found that the actual change from one specific type of pneumococcus to another may be brought about in the test tube outside the animal body.

The experimental evidence now available seems to indicate that any R strain of pneumococcus has potentially the function of elaborating any one of the specific capsular polysaccharides;—the particular one being determined by a particular stimulus of a specific nature. Aloway has recently found that this potential function latent in the living R cells may be specifically activated by the addition to an appropriate medium of a bacterial extract prepared from a given specific type of pneumococcus. Under these conditions, the R forms irrespective of their type derivation again elaborate a capsular material identical in specificity with that of the type of pneumococcus from which the extract was prepared.

There is at present no certain proof that transformations of this kind ever occur spontaneously in nature. Nor is there as yet any epidemiological or clinical evidence that this form of reversible adaption is a factor in the origin of human infection. However, the experimental evidence leaves no doubt that the non-invasive, non-encapsulated R cells under favorable circumstances are potentially capable of again developing into highly virulent organisms and that the acquisition of virulence is invariably associated with the restoration of the function of elaborating the specific capsular carbohydrates. Indeed, it is most significant that no matter whether one considers pneumococcus from the viewpoint of virulence, antigenicity, or its capacity to undergo variation, the single determining factor associated with all these characters is the function of synthesizing the specific capsular polysaccharides. Scarcely less important is the fact that the immunological specificity of each of the specific types of pneumococcus depends upon the chemical individuality of the particular carbohydrate in the cell capsule.

As chemical substances, separate and apart from the bacterial cells, these carbohydrates have been found to incite specific reactions in the tissues of sensitized animals and in the skin of patients convalescent from pneumococcus pneumonia. Guinea pigs passively sensitized with the precipitating serum of an immune rabbit suffer violent anaphylactic shock and die within three to four minutes following the intravenous injection of as little as .055 mg. of the homologous polysaccharide. The anaphylactic reactions are strictly type-specific. There is now ample evidence to support the view that protein-free, even nitrogen-free, carbohydrates may induce acute anaphylaxis in specifically sensitized animals.

Tillett and Francis have found that the injection of 0.01 mg. of specific polysaccharide into the skin of patients recovering from pneumococcus pneumonia may evoke an immediate local reaction in the form of a wheal surrounded by a zone of erythema. The cutaneous reactions develop rapidly within fifteen minutes and subside completely in from one to two hours; they are elicited only by the specific

polysaccharide derived from the same type of pneumococcus as that causing the infection in the patient. The capacity of the skin to react to the specific bacterial sugar is intimately associated with recovery and closely parallels the occurrence of type-specific antibodies in the patient's serum. The results indicate that this specific skin test has prognostic significance and may become of value in determining the therapeutic dosage of antipneumococcus serum.

Studies on "synthetic antigens" prepared by chemically combining derivatives of glucose and galactose with proteins have shown that even these simple sugars exert a determining influence on the immunological specificity of compounds of which they form a part. The newly acquired specificity of these artificially conjugated sugar-proteins is in each instance determined by the chemical structure of the carbohydrate irrespective of the protein to which it is attached. It is especially significant in the case of glucose and galactose that the two sugar derivatives differ from each other only in the spatial arrangement of the hydrogen and hydroxyl groups on a single carbon atom. It is a remarkable fact that the mere rotation of this carbon atom through an angle of 180° suffices to change completely the antigenic specificity of two substances otherwise chemically identical. In the case of these artificially prepared sugar-proteins, the two isomeric sugar derivatives can be selectively differentiated one from the other by serological methods. These observations on the immuno-chemistry of carbohydrates confirm the original studies of Landsteiner on the specificity of azo-proteins and furnish additional evidence of the general dependence of immunological specificity upon the chemical constitution of the reactive substances. It is evident, therefore, that simple sugars, which by themselves are non-antigenic, may, when coupled to a protein, specifically determine the immune response of treated animals, and that the antibodies thus engendered reflect the orienting influence of the sugar radical on the specificity of the antigen as a whole.

From these results we were led to test the possibility of "synthesizing" an artificial bacterial antigen. For this purpose the capsular polysaccharide of type III pneumococcus was chosen, since it contains no nitrogen and in its present state of purity may be regarded as a definite chemical entity. Moreover, if results were obtained with this particular polysaccharide they would be the more significant, since the free substance by itself has never been found to elicit any immune response in rabbits and even the original bacterial cells from which it is derived fail in a majority of instances to incite specific antibodies in these animals. From a chemical point of view, the difficulty lay in synthesizing the appropriate derivative of this complex sugar. It must be one capable of being coupled to protein and one in which the chemo-specific groups of the polysaccharide are not masked by the chemical procedures. Dr. Goebel succeeded in synthesizing the amino-benzyl-ether of the type III polysaccharide and in coupling the diazonium derivative with a foreign protein, namely, the globulin from horse serum.

This soluble antigen therefore has in common with type III pneumococcus only the specific capsular polysaccharide. Rabbits injected with this artificial antigen uniformly developed in their serum type-specific antibodies. The antiserum thus produced not only precipitates the original polysaccharide but agglutinates living cultures of type III pneumococcus and protects animals against infection with virulent organisms of the homologous type.

Knowledge of the chemical nature and significance of the capsular polysaccharides in pneumococcus infection and immunity led us to search for enzymes capable of decomposing these specific carbohydrates. A number of enzymes of animal and plant origin as well as cultures of various bacteria, yeasts, molds and soil actinomycetes, many of which were known to decompose cellulose and other complex carbohydrates, were tested without success. My associate, Dr. Dubos, isolated from peat soil a bacillus which possesses an enzyme that acts specifically on the capsular polysaccharide of type III pneumococcus. From these bacilli the active enzyme has been extracted in soluble form. By technical procedures, active preparations of the enzyme have been purified and concentrated without appreciable loss in potency.

In view of the marked differences in the chemical composition of the various capsular polysaccharides, it is not surprising to find that the enzyme decomposes only the type III substance and has no effect upon any of the other bacterial sugars thus far tested. In this respect, the selective action of the enzyme is as specific as in the immune reaction between the type III polysaccharide and its homologous antibody. The polysaccharide acted upon by the enzyme loses its serological specificity and is no longer precipitable by type III antipneumococcus serum. This enzyme not only acts on the chemically isolated sugar, but it specifically decomposes this substance in the native form in which it exists in the capsules of the living cells. When a sterile solution of active enzyme is added to a growing culture of type III pneumococci, the organisms lose their specific agglutinability and the soluble capsular polysaccharide is serologically no longer demonstrable in the culture fluid. Under these conditions, the enzyme decomposes the capsular substance as rapidly as it is formed without impairing the viability of the decapsulated organisms.

The action of the enzyme does not result in a loss of the function of elaborating the capsular substance, since pneumococci so treated promptly regain their capsules when transferred to an enzyme-free medium. The active enzyme, therefore, represents a specific agent which by itself is neither bactericidal nor bacteriolytic but which, by decomposing the capsular structure, completely alters the biological behavior of the bacterial cell.

In view of these findings, experiments were carried out to determine whether the enzyme would favorably influence the course of experimental infection in mice with type III pneumococcus. It was found that a single injection of an active preparation of enzyme protected mice against infection with a million times the number of virulent organisms invariably fatal

in the untreated animals. The protective action of the enzyme is type-specific; just as in the test tube it decomposes only the type III polysaccharide, so in the animal body it is effective only against infection with type III pneumococcus.

Experimental evidence indicates that in mice the enzyme also has a curative action when administered in the course of an infection already well established at the time of treatment. The administration of the specific agent as late as eighteen hours after the onset of infection has brought about the recovery of mice infected with multiple lethal amounts of a virulent culture of type III pneumococcus. Experiments carried out in collaboration with Dr. Goodner and Dr. Dubos have shown that the enzyme also has a marked curative action in the disease brought about by infecting rabbits intradermally with a highly virulent strain of type III pneumococcus. The experimental disease is characterized by the rapid development at the site of inoculation of an intense inflammatory lesion with spreading edema, marked cellular infiltration and hemorrhagic necrosis, accompanied by fever and the early invasion of the blood stream with increasing numbers of pneumococci. The infection ordinarily terminates fatally within three to four days in 95 per cent of untreated rabbits. Following the intravenous injection of an adequate amount of active enzyme the bacteremia promptly disappears; the local lesion, freed of bacteria, undergoes the natural processes of healing, and recovery occurs in 95 per cent of the animals so treated.

The experimental results support the view that the primary action of the enzyme lies in its capacity to decompose the capsular polysaccharide of the invading pneumococci. The process of decapsulation brought about by the direct action of the enzyme strips the bacteria of their capsular defense and thereby exposes their naked and unprotected bodies to direct attack by the phagocytes of the host. Thus phagocytosis, ineffective against the encapsulated forms, now becomes the important mechanism in the final destruction of organisms from which the capsular substance has been removed by the action of the enzyme.

In this sense, the enzyme may be said to initiate a protective reaction, the successful issue of which depends upon the effective phagocytic response of the host. For these reasons, it at once becomes apparent that the curative action of the enzyme is subject to the limitations imposed by the variations that occur in the cellular defense of the infected animal.

These studies suggest that the capsule—long recognized as a defense mechanism on the part of virulent bacteria—is a decisive factor in determining the fate of pneumococci in the animal body and that this structure is vulnerable to attack by agents other than specific antibodies.

Presentation of the John Phillips Memorial Prize*

By S. Marx White, M. D.
President of the American College of Physicians

Dr. Avery, Fellows of the American College of Physicians, Associates and Guests:

John Phillips was born in Welland, Ontario, February 18, 1879. With a personality marked by simplicity, directness, poise and a remarkable sense of relative values, he came in the fifty years of his life to a high place in medicine in this country. Work was his philosophy of life. He exemplified this, called by Osler the Master Word. His intimate friends tell us he appeared not to know how to play. His contributions to medicine and its literature were many, and were scholarly and sound. Elected to the Board of Regents of the American College of Physicians in 1923, he was active in its affairs in many and important ways. He arranged the programs for the Annual Sessions in Cleveland in 1927.

Valuable as we who knew him held his life to be, he held it as naught if it was needed in the succor of others. When disaster visited the Cleveland Clinic in 1929, he, Chief of Medicine, without thought of self, labored to save its victims. Giving his life on May 15, 1929, he left us a glorious example. The college has founded this annual prize to perpetuate his memory.

The purpose of this prize is to encourage work adding to our knowledge in Internal Medicine, this including not only clinical science but in addition all those subjects which have a direct bearing upon its advancement.

When in one of the Hippocratic writings, "The Law", we read, "There are in effect two things, to know and to believe one knows; to know is science; to believe one knows is ignorance", we are on the threshold of the conception of medicine as an art based on accurate observation, and as a part of the science of man. When many centuries later we follow William Harvey and René Descartes in "la nouvelle methode" of experimental science, we are preparing to wrest from nature some of her profoundest secrets. Induction, intuition, and deduction, served by the sometimes slow, painstaking methods of trial and error, lead us to an understanding of nature never suspected by the ancients. But here again we glimpse what they so plainly saw, "Life is short and the Art is long". Fifty years have passed since Robert Koch discovered the bacillus of tuberculosis. The conquest of the disease, though well under way, is not yet complete. In the meantime, yellow fever has been eliminated from the

*April 6, 1932.

civilized world, through the efforts of a devoted band of scientists with its martyrs, even though the causative organism may be yet in doubt. Illustrations need not be multiplied.

Fifty years have passed since Friedländer found that capsulated cocci were present constantly in the exudate of pneumonia, and two years after that, Fraenkel demonstrated the causative relation of the pneumococcus to the disease. Our conquest of pneumonia has scarcely begun. We are beginning to see it as through a glass, darkly, however. All honor then to the men, who step by step, are treading the paths that will eventually lead to the hiding place of the pneumococcus, and who by the processes of science, though they be slow and painstaking, are discovering how to strip it of its protective covering.

The committee having in charge the award, in seeking a candidate, selected an advisory group of sixteen members of the College, each prominent in some certain aspect or field of medicine. The suggestions made by each of these, and by the members of the committee, were listed and then sent out to the two groups, with the request that each man would indicate his first, second and third choice from amongst that list. Twenty-five of the votes went to Dr. Avery.

The committee, therefore, through its chairman, Dr. James H. Means, recommends the award, "To Dr. O. T. Avery for the series of studies upon the pneumococcus in which he has played a leading rôle, beginning with the discovery of the type specific soluble capsular polysaccharides and culminating in the discovery of a bacterium producing an enzyme which splits the polysaccharides of type III pneumococcus in vitro, thus rendering it susceptible to phagocytosis and thereby protecting the animals which are infected with it". Dr. Avery, you are the first recipient of this annual award. As evidence of appreciation of your industry, your devotion to Science and your scholarly attainments we present you, in the sum of $1500.00, with this, the John Phillips Memorial Prize of the American College of Physicians.

Physical and Physiological Aspects of Arteriosclerosis and Hypertension*

By Carl J. Wiggers, M.D., F.A.C.P.,
Cleveland, Ohio

Introduction

THE subjects of arteriosclerosis and hypertension have been extensively studied and even more extensively discussed by the clinician, pathologist, therapeutist and experimentalist, each naturally, according to his own point of view. But results of physical and physiological investigations have been more or less entombed in library stack-rooms; at least to my knowledge they have not been reviewed in such a form as to make the facts easily available.

My own venture in attempting to review a topic in which so many gaps still exist is actuated by our need for survey of the known physical and physiological consequences of arterial disease. Such an adventure is of triple value: it places the essential known facts in orderly array, it reveals the gaps and questionable evidence and supplies a working basis from which new physiological investigations may proceed. Indeed, such a systematic survey and critical evaluation of existing theory and fact forms a natural prelude to an interpretation of those experiments which Nature chooses to make on animals and man, and which are designated by the term, Disease.

Physiological Factors in Hypertension

Two primary vascular changes may be concerned in hypertension, viz., (a) alterations in the elastic properties of the large arteries which serve as physical buffers to the capillary flow and (b) changes in the lumen and resistance of the smaller arterioles which act in the capacity of stopcocks regulating the outflow from the arterial tree. In addition, secondary changes in the action of the heart supervene and complicate the dynamic picture. When, as in this instance, the heart and circulation are affected by a number of different factors it becomes confusing, if not quite hopeless, to evaluate the share that each element contributes. In such instances, physiologists frequently adopt the expedient of studying the changes in the heart and circulation when only a single factor alters at a time. We shall utilize this method in analyzing the hypertension problem.

*From the Department of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio. Read before the American College of Physicians, San Francisco, April 6, 1932.

The Evaluation of Arterial Elasticity

Studies on Excised Vessels. The elasticity of tubular structures such as arteries is usually determined by measuring the increase in cubic contents when the internal pressure is raised a definite amount. The ratio, pressure increase to volume increase ($\frac{dp}{dV}V$), is designated *the volume elasticity coefficient* (E_v). Obviously, such a coefficient increases inversely as elasticity and directly as rigidity.

Physical tests have demonstrated that arteries are not equally distensible at all internal pressures; on the contrary, their distensibility decreases progressively as internal pressure is raised. A curve in which pressures as abscissae are plotted against volumes as ordinates therefore assumes a hyperbolic form, convex to the abscissae (figure 1, A). When medium sized arteries, such as the carotid, brachial or radial are studied, it is often found that the reactions differ both quantitatively and qualitatively in repeated tests. Two other forms of curves, illustrated by B and C in figure 1, are often obtained. Each of these has, indeed, been advocated as representing the true volume-elasticity curve of arteries. MacWilliam (1902) concluded that these variations are due, in large part at least, to variable degrees of muscular contraction. According to his studies, moderate muscular contraction hinders stretching at lower internal pressures only, hence the elasticity coefficient follows an S-shaped curve (B). If, however, the vessels are firmly contracted, the muscular force opposes distention at all ranges of internal pressures, hence a straight line or concave elasticity curve (C) is the result. It is obvious that the excursion of peripheral arteries such as the radial and perhaps the brachial may not be governed solely by internal pulse pressure variations but by the degree of muscular contraction as well.

When an artery becomes less elastic through sclerotic processes or chemical

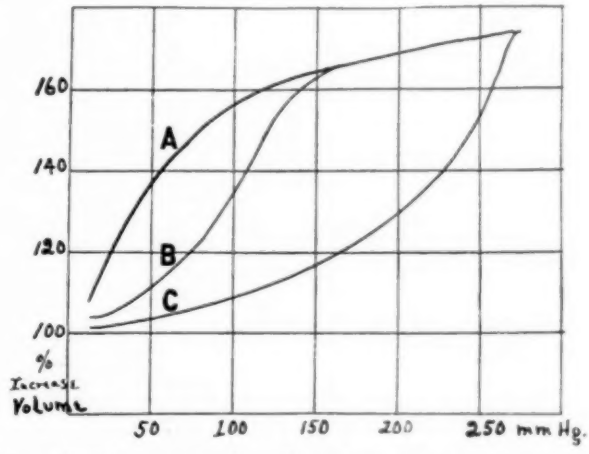


Fig. 1. Volume elasticity curves of medium sized arteries: A, relaxed vessels; B, moderately contracted vessels; C, strongly contracted vessels.

treatment, its distensibility under equivalent pressures is not merely decreased but the form of the extensibility curve also changes. Obviously some other factor, that may be spoken of as the elastic "personality" of the vessel, is altered.

Frank (1927) designated this by q in the equation $E = E_0 + q\sigma^2$, in which E_0 denotes the residual elastic resistance of unstretched vessels and σ the specific tension per unit cross-section area.

After mathematical treatment of the problem (1920, 1928) Frank (1927), in association with Mays and Hochrein, reported experiments on rings of aortas obtained post-mortem from individuals of different ages. Such central vessels have the advantage of giving constant responses because the experiments are not complicated by the effects of muscular contraction. These data have been plotted, using E values as ordinates and σ values as abscissae (figure 2). A glance shows that in young persons arterial rigidity (E) increases very little at lower tensions but trends rapidly upward at higher tensions (σ). In case of aortas from older subjects, on the contrary, the lines begin to curve upward at progressively lower tensions and, moreover, rise with a steeper gradient until in very old age they become almost straight lines from the start. Such curves indicate that while the residual elasticity of arteries (E_0) does not alter with age, their extensibility decreases rapidly with increasing tensions and more especially at lower tensions. Graphs such as these give a qualitative and objective picture of the changes concerned in ageing of the arteries. Since the coordinates of each curve can be expressed mathematically as a rational function of their parameter—i.e., q in Frank's formula—it is possible to cal-

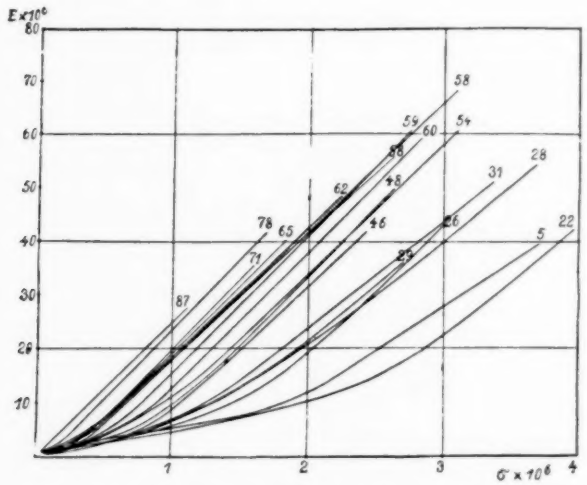


FIG. 2. Curves showing the elastic coefficients (E) of aortas at different specific tensions, (σ) at ages directly indicated on the chart. E and σ, expressed in 10^6 dynes, a unit which corresponds approximately to pressure exerted by an atmosphere per cm.^{2} (after Frank).

culate values for q* and to express the age characteristics in a quantitative fashion, as in figure 3. A consideration of such graphs led Frank to the conclusion that while the residual elasticity (E_0) scarcely alters with age extremes (5-87 years) the parameter q increases more than sixfold.

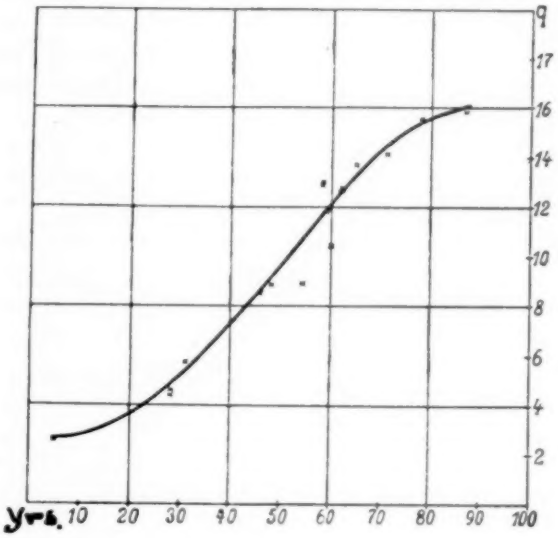


FIG. 3. Curve expressing mathematically the elastic characteristics *(q)* of the aorta at different ages (abscissae) (after Frank).

It can safely be predicted that systematic use of this method in post-mortem studies of large arteries from subjects who had arteriosclerosis and hypertension would yield part of the information still needed to explain both the cause and the dynamic effects of hypertension.

Studies on Vessels in Situ. According to the classical formula of Moens ($V = K\sqrt{g\frac{E.a}{s.d}}$) the pulse wave velocity (V) varies directly as the square root of gravity (g), the elasticity coefficient (E), and the arterial wall thickness (a), and inversely as the square root of the specific gravity of blood (s) and the diameter of the vessel (d). Assuming all factors except E to remain constant or to be inconsequential, an inverse relation obviously exists between pulse velocity and arterial elasticity.

It is therefore not surprising that many investigators have attempted to study the elastic condition of arteries *in situ* by measuring pulse velocities. While there appears to be general agreement in the conclusion that the pulse velocity progressively increases with age, an examination of the many

*Since the parameter q has no absolute value it has been given the arbitrary value 1.5 when specific tension equals 1.5×10^6 dynes. The formula expressing the elasticity coefficient at this pressure then becomes $E_{1.5} = E_0 \times \sigma_{1.5}{}^2$.

data upon which such statements are based reveals many discrepancies both as to what constitutes a normal velocity and as to the magnitude of the increase with age. Figure 4 shows velocities reported by three groups of workers in comparison with values calculated by Frank on the basis of elasticity studies of human aortas. The great differences shown require no further comment. Likewise, while the majority of observers claim that the pulse is propagated faster in cases of demonstrated arteriosclerosis, nephritic hypertension, etc. (Friberger, 1912; Münzer, 1912), Sands (1925) was unable to corroborate these results. My own observations confirm the conclusion that the pulse velocities encountered in patients with hypertension certainly fall within the ranges found yearly in young, healthy medical students.

The variable results arrived at by different investigators are partly due to the methods and procedures employed in estimating pulse velocities; partly also to the fact that pulse velocity is affected by the size of vessels (Bazett and Dryer, 1922; Sands, 1925) and by the height of diastolic pressure (Frank, 1927; Bramwell, Hill, McSwiney et al., 1922-1923). Improvements in technical methods for pulse registration have reduced to a minimum the errors incident to accurate calculations of pulse delay between two points. Unfortunately, it remains just as difficult to measure with exactness the arterial distance traversed by the pulse wave. The possibility of error thus introduced becomes even greater when vessels are tortuous. The variations in size of vessels resulting from muscular contractions or pathological processes are also beyond our present means of study and evaluation (cf. Lyon and Sands, 1924).

Bramwell, Hill and McSwiney (1922, 1923, 1924) have made earnest attempts to take variable diastolic pressures into account and to this end have

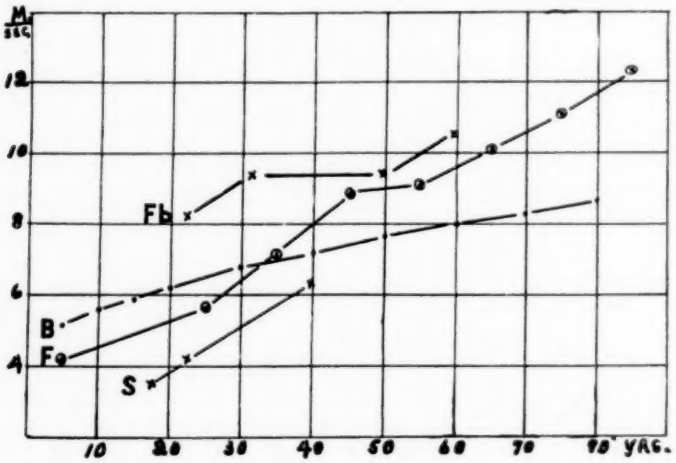


FIG. 4. Chart giving pulse velocity data at different ages according to Friberger (Fb), Bramwell and Hill (B), Sands (S), compared to calculated velocities of Frank (F) for internal pressures of 100 mm. Hg.

introduced an ingenious yet simple method by which the *effective* diastolic pressure in a short length of artery can be altered at will. This was accomplished by applying a positive or negative counter pressure over a brachial or radial artery through an elastic cuff or chamber and calculating the velocity of the pulse wave in the short length of vessel submitted to such positive or negative pressures. In this way, the pulse velocities at pressures above and below existing diastolic pressures could be calculated according to the formula

$$V = \frac{d}{y\text{-}x\ \frac{(1\text{-}d)}{l}}$$

where x equals transmission time between two points distant *l* from one another and *y* the time between same points when a bandage of length *d* is applied. By applying a simplified formula,

$$\text{percentage increase in volume per mm. rise of pressure} = \frac{12.7}{\text{Velocity in meters/sec.}},$$

the extensibility at different diastolic pressures could be determined and plotted in the form of curves. Finding good agreement between average velocities in vessels *in vivo* and others on isolated arteries, Bramwell, Hill and associates concluded that it is possible to evaluate changes in elasticity of vessels *in situ* by such means.

The method, however, appears to have several shortcomings: (1) The actual length of artery compressed and hence the pulse velocity in it cannot be determined with great exactness; (2) the extensibility curve derived applies only to the vessel examined and not to the aorta or arterial system as a whole; and (3) the extensibility curves of similar arteries are apparently not the same in normal individuals. Thus, Hemmingway, McSwiney and Allison (1928) recently found great differences, both in pulse velocities and extensibilities of normal brachial arteries. A series of these curves, reproduced in figure 5, indicates that the arteries of normal individuals fall into three groups, viz., super-extensible (S), normal (N) and hypo-extensible (H) and furthermore that the mean pulse velocity at corresponding effective pressures (lower set) varies a great deal.

I have set forth briefly the difficulties that discourage the use of pulse velocity determinations in evaluating the elastic state of vessels *in situ* not with the purpose of detracting from the sincere attempts made to overcome great physical difficulties, but rather to give you an idea of the obstacles that still remain to be surmounted.

The Functional Nature of Increased Peripheral Resistance

Morphological changes in the peripheral arterioles with reduction or obliteration of their lumen rarely if ever account entirely for the increased peripheral resistance encountered during hypertension. Endarteritis is rarely universal; not infrequently it is limited to individual organs such as the kidneys, pancreas, spleen, etc. Moreover, even after mechanical deletion of large portions of the natural circu-

lation, physiological compensatory mechanisms, both nervous and mechanical, are able to reestablish arterial pressures at approximately normal levels. For example, it is possible in dogs to ligate one common carotid, both subclavian and internal mammary arteries and, in addition, the aorta above the renal arteries without causing a rise of blood pressure that lasts more than ten or fifteen minutes.

Consequently, the conclusion appears justified that increased peripheral resistance sufficient to bring about prolonged or permanent elevation of pressures must be due either (a) to excessive generalized functional contraction of arterioles or (b) to failure of the reflex mechanisms which normally moderate blood pressures. The agents which cause such vascular constriction and the mechanisms involved remain shrouded in mystery; indeed, it is not improbable that they are many and varied. Time is lacking to review the many chemical, hormonal and nervous theories that have been advanced to account for the generally contracted state of peripheral arterioles. Fortunately, this is not vital, however, as the reader may refer to the excellent monograph of Gager (1931) for a discussion of this aspect of the subject. The possibility that unbalanced reflexes rather than specific chemical stimulations of arterioles or their controlling nerve

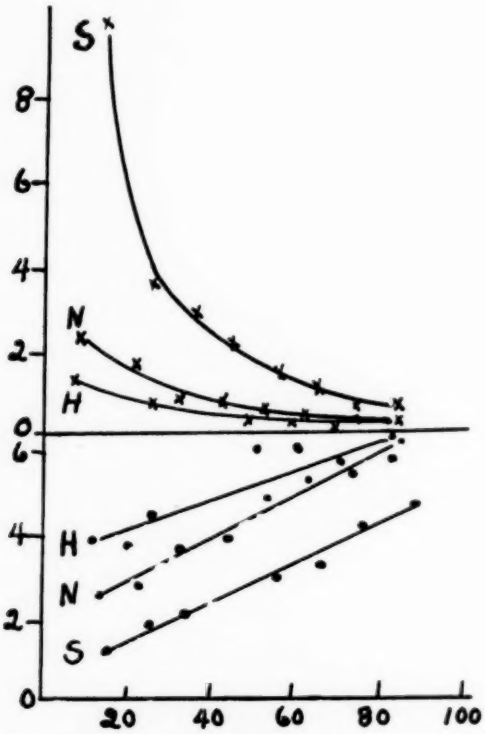


FIG. 5. Graphs showing arterial extensibility (upper curves) and pulse velocities (lower curves) in normal individuals at effective diastolic pressures indicated on abscissae. S, super-extensible type; N, normal type; H, hypo-extensible type—(after plots from McSwiney et al.).

centers may play a rôle in some forms of human hypertension is suggested by recent experimental work. Denervation of the sinus caroticus and section of aortic nerves can provoke a state of hypertension accompanied by notable increase in cardiac size (Koch, Mies and Nordman, 1927; Regniers, 1930). Mechanical obstruction to flow in abdominal viscera and perhaps in the heart may likewise set vasomotor reflexes in operation which if uncompensated may result in persistent hypertension (cf. Hering, 1930).

Hemodynamic and Cardiodynamic Effects of Increased Arterial Rigidity

Arterial Pressures and Flow. Mathematical calculations and physical experiments lead to the conclusion that increased rigidity of large blood vessels causes an elevation of systolic and a decline of diastolic pressures at a constant cardiac rate and output. The arithmetical mean pressure is reduced somewhat. Fahr, Davis, and Spittler (1931) have demonstrated that similar changes occur in a heart-lung preparation so arranged that the volume-elasticity coefficient of the arterial system could be increased or decreased at will. However, the pressure changes reported were doubtless exaggerated a great deal through the maximum and minimum valved mercury manometers employed.

I have recently reinvestigated the circulatory effects produced when the elasticity of the aorta was decreased by treatment with formalin. The aorta from a large dog, after removal from the body and ligation of all branches, was inserted into an artificial circuit in which pressure variations resembling those found in normal animals were reproduced artificially. In such a system the pressure head, heart rate, periods of ejection and peripheral resistance could be kept constant while the elasticity of the aorta was changed by perfusion with formalin solution. Optically recorded pressure curves before and after formalinizing the aorta are shown in segments D, E and F of figure 6. They demonstrate that the more rapid decline of pressure during diastole and the consequent lowering of diastolic pressure are the only changes as long as the pressure head remains constant. The explanation is simple. Through a reduced expansion of the aorta by an equal pressure head, less blood is accommodated during mechanical systole and a larger volume moved forward. Consequently the tubes contain less fluid at the beginning of mechanical diastole and reach their normal state more rapidly, with the result that arterial pressure falls quickly and to a lower level. The stream distal to a peripheral constriction, i.e., in the capillaries, becomes less and less constant as elasticity diminishes and with very rigid vessels acquires a pulsating character. The minute flow also decreases. Such physical experiments demonstrate how a capillary pulse and collapsing arterial pulse can be dynamically produced without change in peripheral resistance or without occurrence of valvular insufficiency. The practical conclusion is derived that the collapsing character of clinical pulses during aortic insufficiency becomes greatly intensified when sclerosis of the aorta coexists.

Dynamic Effects on Left Ventricle.

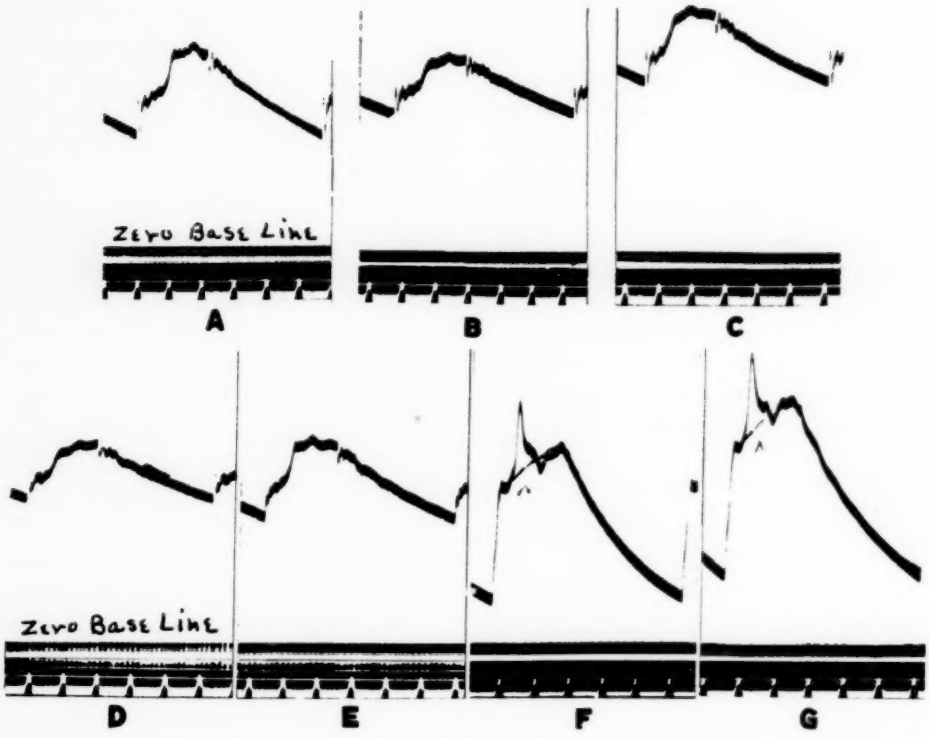


FIG. 6. Aortic pressure curves from a dog's aorta in an artificial circulation machine. A, control conditions, minute volume, 630 c.c.; B, after increased peripheral constriction, minute volume, 350 c.c.; C, after raising pressure head, minute volume, 420 c.c. D, same conditions as B; E, 10 minutes after applying formalin to aorta, minute outflow 290 c.c.; F, 3 hrs. after formalin treatment, minute outflow 240 c.c.; G. same conditiins as F. but with increased systolic pressure head, minute outflow 310 c.c. Peaks x are accentuated waves (possibly reflected waves) superimposed on fundamental forms. Time 1/5 sec.

The total internal energy transformation during each heart beat is largely degraded into heat, less than 20 per cent manifesting itself as useful external work.

The work of the left ventricle is conveniently, though somewhat roughly, calculated as the product of mean pressure and quantity of blood ejected. Using such a formula, Fahr, Davis and Spittler (1930-31) concluded from experiments on heart-lung preparations that since neither factor changed significantly, the external work of the heart is practically unaffected through an increased elasticity coefficient of the arterial system.

The total energy utilization can be found directly only from studies of oxygen consumption by the heart. Such determinations still need to be made. Starling and Visscher (1927), however, observed quantitative relations between changes in oxygen consumption and diastolic size and Fahr et al. (1931) noted that the diastolic size remained unaltered when the volume elasticity coefficient of the arterial system was increased. Therefore they tentatively concluded that the total en-

ergy consumption of the heart is little, if at all, affected.

These deductions, however, square neither with *a priori* considerations nor with physical experiments. Any augmentation of arterial systolic pressure obviously presupposes a corresponding elevation of left ventricular pressure. It is difficult to visualize how this can come about without additional expenditure of energy if, as experiments indicate, systolic discharge remains the same. Physical tests show definitely that the minute volume flowing through less elastic tubes can be restored to normal only by increasing the pressure head. Thus in the experiment illustrated by segments D, E and F, figure 6, the minute outflow decreased progressively from 340 to 240 c.c., but by elevating the pressure head and thereby both systolic and diastolic pressures as shown in segment G the outflow was increased again to 310 c.c. The faultiness of Fahr, Davis and Spittler's recent conclusions appears to arise from use of an arithmetric mean pressure in calculating the work of the left ventricle and in ignoring entirely the velocity factor. Katz (1932) has recently again pointed out how great and variable the error may be, even when mean pressure and mean velocity are both used in work calculations. The tendency is to under-estimate both the pressure and velocity energy and to alter their distribution so that the per cent calculated as kinetic energy seems less than it really is. On a previous occasion Fahr (1927) himself recognized that such calculations are only approximations and suggested the integral

$$\int_{P_1}^{P_2} \text{pvd} + \frac{sv^2}{2g}.$$

Using this integral, Fahr (1927) also arrived at the conclusion on theoretical grounds that arteriosclerosis increases the work of the left ventricle but only insofar as it necessitates increased systolic pressures.

A critical evaluation of existing theory and fact therefore makes it improbable that an increased elasticity coefficient of the aorta is without effect on the total energy expenditure or external work of the left ventricle, though it is probable that the magnitude of the increase need not be very great with the degree of rigidity ordinarily attained.

Hemodynamic and Cardiac Effects of Increased Peripheral Resistance. Increased arteriolar resistance affects hemodynamics primarily by reducing the minute efflux from the arterial system. As a result, systolic and diastolic pressure are both elevated and the amplitude of the pressure variations is reduced. In other words, the effects on pulse pressure are just the reverse of those produced by decreased elasticity of large vessels. The significance of the physical changes in systolic and diastolic pressures are demonstrated by experiments on a dog's aorta. As shown in figure 6, A and B, augmented peripheral resistance decreases the rate at which pressure declines during diastole and elevates the diastolic pressure when the pressure head (i.e., systolic pressure) is kept constant. Coincident with these changes in pressure the peripheral outflow decreased from 630 to 350 c.c. per minute. When the pressure head is elevated, both systolic and diastolic pressures rise together but the pulse pressure still remains less than normal. As illustrated in figure 6, C, even this elevation of

pressure head was unable to restore the minute outflow to normal, for it was only 420 c.c. per min. at the time this tracing was recorded. Such physical experiments demonstrate clearly that the rise in diastolic pressure reflects primarily the magnitude of the peripheral resistance change and that a considerable elevation of systolic pressure is needed in order to restore the capillary bloodflow to normal.

The manner in which the heart accomplishes this can fortunately be studied in animals whose peripheral resistance is acutely increased either mechanically by compression of the abdominal aorta or more physiologically by generalized vasoconstriction. The latter is easily accomplished reflexly by stimulating the central end of a vagus nerve. The changes in central pressure pulses produced by such stimulation are illustrated by segments A, B and C in figure 7. We note that contrary to physical experiments, the pulse pressure increases and that systolic pressure rises more than diastolic. The preliminary vibration (a) occurring during the isometric periods becomes more intense and the height of the primary upstroke (b) increases. All of these characteristics clearly indicate that the ventricular contractions were more vigorous.

The mechanisms by which this is accomplished were studied by Katz and myself.* These investigations demonstrated that increased peripheral resistance causes an immediate but transient decrease in systolic discharge

*For details cf. Wiggers, Circulation in Health and Disease, 1923, p. 113; Pressure Pulses in the Cardiovascular System, 1928, p. 132.

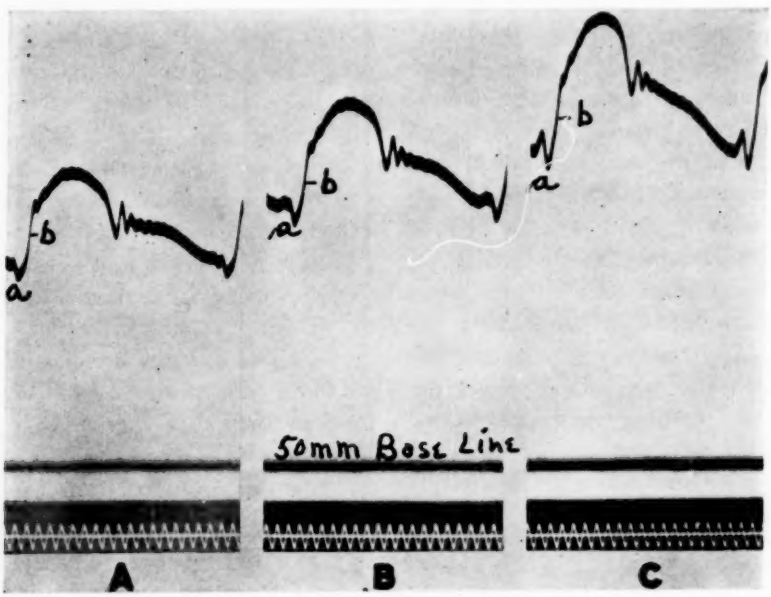


FIG. 7. Subclavian pressure curves recorded by optical manometer from a dog. A normal pressure pulse; B and C at various stages during increased peripheral resistance produced by central vagus stimulation. Time .02 sec.

with the conversion of more kinetic energy into pressure energy. The residual blood which thus accumulates from beat to beat, added to normal inflow from the left auricle, quickly increases diastolic ventricular size and elevates the initial tension. This acts as a stimulus to cardiac muscle, in consequence of which systolic volumes again equal or even exceed the normal, depending on the intensity of the peripheral change.

Wiggers and Katz (1928) have further studied how the economy of ventricular effort is affected under such conditions. This was done by determining the ratio between the static effort and dynamic effort of the left ventricle during the period of ejection. To do this, we calculated by analysis of optical pressure curves how much of the total pressure energy during the ejection period is required to support the arterial pressure in the aorta statically and how much is stored during systole for conversion into energy of flow during subsequent diastole. Our results show that increased arterial resistance not only augments the external work of the heart but also decreases the economy of effort. We also found, however, that the increased diastolic size and initial tension supplies a mechanism whereby the economy of effort is approximately restored to normal.

Summarizing, the accumulation of residual blood which temporarily follows increased peripheral resistance acts successively to increase the diastolic size and initial tension and to restore both the systolic output and the economy of effort to normal. Through these physiological compensatory mechanisms systolic arterial pressure is elevated until the capillary volume flow is again normal.

Physiological Factors in Cardiac Hypertrophy

Growth implies increased metabolism. Increase in bulk of muscular elements, i.e., hypertrophy, must therefore be preceded by increased metabolic rate. The experimental results of Starling and Evans and Starling and Visscher make it extremely probable that, as far as the heart is concerned, oxygen consumption is related solely to changes in diastolic volume. Hence, of the many theories proposed to explain cardiac hypertrophy, the conception that it is caused by a previous increase in initial tension and diastolic stretch appeals most to a physiologist. Since only a moderate increase in peripheral resistance is required to produce such changes in diastolic size and since the elasticity coefficient of the larger vessels must be considerably augmented to effect a much smaller ventricular distention, the conclusion follows that alteration in caliber of peripheral vessels is ultimately the predominant factor responsible for the left ventricular hypertrophy so common in patients with persistent hypertension.

This is not the occasion to discuss the many theories proposed to explain ventricular hypertrophy. It may be stated in passing, however, that the view of Holman (1925) which associates hypertrophy with movement of increased minute volumes by the ventricle, certainly cannot account for hypertrophy secondary to hypertension. Neither animal experiments nor

observations on patients with hypertension give any evidence that the minute volume is significantly increased (see below).

Hypertrophy is so commonly regarded as a pathological and harmful process that its beneficial character is generally forgotten. The physiologist looks upon hypertrophy as a normal functional response to increased stretch, regardless of whether this is secondary to physiological or pathological changes in the circulation. In a sense, the normal left ventricle is physiologically hypertrophic. At birth the weights of the two ventricles are very nearly equal but, owing to a progressively greater peripheral resistance and diastolic stretch, the left ventricle slowly increases in bulk. The question may therefore be raised whether an additional increase in left ventricular bulk during hypertension cannot also be considered a physiological rather than a pathological reaction. It is true that deleterious influences primarily responsible for changes in diastolic size and hypertrophy may also effect the myocardium, producing structural differences in heart muscle cells which are superadded to, but not fundamentally a part of, the hypertrophic process *per se*.

The Physiology of Clinical Hypertension

By far the majority of clinical investigators are rapidly arriving at the conclusion that changes in arteriolar resistance are mainly, if not solely, responsible for the hemodynamic alterations in clinical hypertension. This view is summarized with great positiveness, for example, by Weiss and Ellis (1930):

> "A satisfactory explanation of the dynamics of the circulation in patients with hypertension is that due to the abnormally accentuated arteriolar resistance, a high arterial and arteriolar pressure is essential to establish the normal capillary bloodflow pressure in the vital organs. The measurements and observations do not bear out the observations that loss of elasticity of the great arteries, or increased cardiac output or increased circulatory volume- - - - - is responsible for the pressure of hypertension."

We have substantial experimental evidence for the conclusion that sclerosis of large central arteries, on one hand, and increased peripheral resistance on the other hand not only affect the left ventricle to different degrees but that they produce directly opposite effects on arterial pulse pressures and diastolic pressures as well. With this as a criterion we may properly inquire whether clinical forms of hypertension fall naturally into two such physiological groups or whether a combination of peripheral and central effects generally obtains. In scanning the records of patients with hypertension in the wards of Lakeside Hospital with the view of selecting certain types for more detailed physiological study I am continually impressed with the fact that the majority of subjects have large pulse pressures and high diastolic pressures. Except when complicated by aortic leaks, the patient with low or even normal diastolic pressure readings is rare indeed. These personal impressions are confirmed by a review of cases of hypertension reported in the literature. Let us take several examples. Hochrein (1928) tabulated 66 cases, exclusive of those with auricular

fibrillation. In 58 of these, pulse pressure exceeded 58 mm.; in 21 cases it ranged between 58 and 80 mm.; in 22 cases, between 80 and 100 mm.; and in 12 cases, between 100 and 135 mm. In none of the 66 instances reported was diastolic pressure below 80 mm. Hg. In 34 cases it was between 99 and 109 mm.; in 21 cases, between 110 and 134 mm.; and in 6, above 135 mm. Similar data from 27 patients reported by S. Weiss and Ellis (1930) reveal pulse pressure ranges from 58 to 80 mm. in 9 cases, from 80 to 100 mm. in 7 cases; from 100 to 145 mm. in 10 cases; and a value of 205 mm. in 1 case. Of these, one had a diastolic pressure of 68 mm.; 8 had diastolic pressures between 90 and 109 mm.; 16 between 110 and 135 mm.; and 2 were 139 and 160 mm., respectively. Twenty-four cases of hypertension tabulated by Feil and Katz (1924) show similar though less pronounced increases. Diastolic pressures were 85 mm. in one case; between 90 and 109 mm. in 4 cases; between 110 and 135 mm. in 10 cases; and between 136 and 175 mm. in 9 cases. However, pulse pressures ranging between 35 and 50 were reported in 7 cases, between 60 and 80 mm. in 9 cases; between 80 and 89 mm. in 5 cases; and between 90 and 110 mm. in 3 cases.

Such uniform and consistent pressure data from patients representing great variety as to etiology, symptomatology and pathology can easily be duplicated from many other sources.

The following simple tabular summary comparing clinical blood pressure observations with experimental reactions in which one factor is varied at a time is interesting:

Blood Pressure Changes in Hypertension

	Experimental increase in rigidity of large arteries	Experimental increase in peripheral resistance	Clinical hypertension
Systolic pressure	High	High	High
Diastolic pressure	Low	High	High
Pulse pressure	Large	Small	Large

It suggests forcibly that the experiments which Nature is accustomed to perform on patients generally combine alterations in elasticity of central vessels with increased resistance in peripheral arterioles; the large pulse pressure being a reflection of the greater rigidity of vessels and the high diastolic pressure, of the peripheral resistance change.

If this is true, subclavian pulse tracings from patients with hypertension should display deviations from normal which resemble those of segments E, F and G of figure 6, rather than those of segments B and C of the same illustration. This accords with my findings in a limited number of patients studied in Lakeside Hospital. Figure 8 shows two sets of such tracings; B and C from patients with hypertension, and A from a normal medical student.

The tracings of curves B were obtained from an individual without palpably thickened arteries and in whom all clinical signs pointed to increased arteriolar resistance as a cause of the high blood pressure. While central and peripheral pulse curves re-

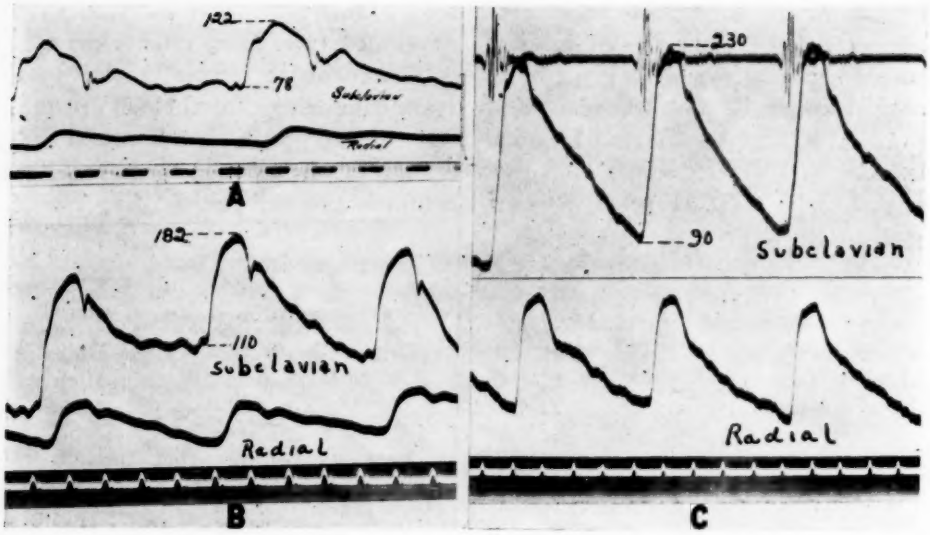


FIG. 8. Three sets of human subclavian pulses (S) and radial pulses (R); A, normal subject; B, hypertension, essentially peripheral origin; C, hypertension, from patient with palpably sclerotic arteries. Systolic and diastolic pressures marked directly on curves in each case. Time in 1/5 sec.

tain many characteristic features of normal curves, the rapid decline of the subclavian pulse curve after the incisura resembles the curve of segment E, figure 6, rather than that of segment B or C. The radial pulse also shows a sharper incisura than it is customary to find in normal pulses. Reflected waves such as are commonly superimposed on normal central pulses (A) are conspicuously absent. Consequently, despite contrary clinical evidence, anyone accustomed to curve analysis cannot conclude otherwise than that some decrease in arterial elasticity must have contributed to the changes in pulse form.

In the great majority of cases examined, however, the evidence is still more conclusive. The records reproduced as figure 8, C, were taken from a man 72 years of age. The subclavian and radial arteries were hard and thickened and the former definitely enlarged. The central subclavian pulse is characterized by the steep ascent, by the short period of systolic ejection, by the altered contour of the systolic summit, but chiefly by the great decline of pressure following the incisura. The curves clearly resemble those of G in figure 6, not those of C in the same illustration.

The radial pulse curves fail to show the customary transformation of the pulse in its transmission to the periphery; on the contrary, its contour resembles remarkably that of the subclavian. The incisura is marked and no dicrotic wave is apparent. Such a propagation of pulse waves to the periphery could be possible only through very rigid vessels.

Summarizing, the large pulse pressures, high diastolic pressures and characteristic pulse curves exhibited by

the majority of patients hospitalized as a result of hypertension definitely favor the view that alteration in elasticity of large vessels modifies and often dominates the hemodynamics of the circulation. This in no wise precludes the coexistence of increased arteriolar resistance, nor does it invalidate the generally accepted belief that the latter is the primary disturbance and chiefly responsible for the cardiac hypertrophy.

Before our conclusion can be finally accepted, however, it is necessary to exclude the possibility that the large pulse pressure and excessively high systolic pressure are not due to an increased systolic output, a possibility that is given extra weight by the facts that a hypertrophied left ventricle exists clinically and that an increased systolic discharge consistently occurs in acute experiments on animals (cf. figure 7). The evidence against such a possibility can be stated briefly.

1. The majority of investigators (Lauter and Baumann, 1928; Burwell and Smith, 1929; S. Weiss and Ellis, 1930; Ernst and R. Weiss, 1929; Hochrein, 1928) have been unable to demonstrate increased minute volumes in patients with hypertension, by means of gasometric methods.

2. The venous pressures do not appear to be elevated (Hochrein, S. Weiss and Ellis) and the blood volumes are apparently not increased (S. Weiss and Ellis).

3. The duration of systole in relation to cycle length is also not increased (Feil and Katz) as might be expected to be the case were the systolic discharge greater.

4. The changes in contour of the central pulse are not those that would be expected were increased systolic discharge the chief factor concerned. It is necessary only to contrast curves of figure 8, B and C, with those of figure 7, B and C, in which changes in systolic output were alone superadded, in order to become convinced on this point.

Careful evaluation of the experimental and clinical evidence therefore leads to the conclusion that the circulatory changes in clinical hypertension are usually produced by the combined effects of increased peripheral resistance and decreased elasticity of the aorta.

Physiological Principles in Treatment. Physiologically, hypertension must be looked upon as a compensatory reaction designed to restore a normal blood supply to the tissues. As already explained, the elevation of systolic pressure is the effective force; while increase of diastolic pressure is largely a resultant of the peripheral and central vascular changes. If the physiological conception that hypertension is Nature's method of assuring an adequate blood supply to the tissues, could gain firmer root in the doctor's mind and through him be relayed to his patient, it would do much to dispel that feeling of despair and impending doom so common in the layman who learns that his blood pressure is "high". Judiciously used, the physiological conception can do much to supplant pessimism by optimism, both in patient and doctor.

The compensatory character of clinical hypertension cannot be ignored in treatment of the condition. Therapeutics as a science is steadily moving

forward. Through birth of the sister science of Pharmacology, the precise modes and places of drug action have become established; drugs with previously assumed virtues have been discarded and others with unrecognized potentialities have been given a place in therapeutics as a result of pharmacological experimentation. However, *the application of knowledge* gained through pharmacological investigations is still guided too generally by allopathic doctrines. Blood pressures are found to be high; the indications are to administer drugs which pharmacological research assures us will lower it—so runs the allopathic philosophy. A great scientific principle is forgotten, viz., that guidance and treatment can ordinarily accomplish no greater good than to assist the compensatory or curative processes that are naturally called into play. Certainly any remedy or agent that thwarts the natural compensatory processes should be employed only advisedly.

The question may now be raised whether it is advisable to lower blood pressures in hypertension unless real dangers appear to be impending. S. Weiss and Ellis justly warn that "therapeutic procedures which lower blood pressure through decreased cardiac output can only be harmful". But the indiscriminate use of vasodilating drugs is equally undesirable. Their effect on blood flow through an organ is always the resultant of two actions, viz., the local change in caliber of vessels and the degree to which pressure is lowered in the aorta. Now it is a fact that vasodilator drugs without exception act predominantly on those arterioles that possess the greatest number of muscle fibers. For example, they affect vessels of abdominal organs more than vessels of the heart and brain, hence the flow through the latter is determined by the change in aortic pressure rather than by local variations in caliber. I have repeatedly demonstrated experimentally, for example, that amyl nitrite, contrary to general belief, reduces bloodflow through the coronary and cerebral vessels.

Obviously such lowering of blood pressure defeats the purpose of natural compensatory mechanisms, and at times may actually be dangerous. An experimental observation may be added to emphasize this statement. When the abdominal aorta of a dog is occluded for an hour or more and the compression then released, aortic pressures fall to very low levels and the animal soon dies of circulatory failure. Erlanger attributed these reactions to shock resulting from prolonged anoxemia of tissues, but my own evidence shows convincingly that the marked fall of pressure is directly due to myocardial failure. Venous pressure rises, it does not fall as in shock; the small cardiac ejections are due to impaired contraction, not to deficient filling as in shock. The reduced coronary flow following the sudden decrease in aortic pressure after decompression is undoubtedly the factor that initiates the myocardial failure. Little imagination is required to suggest how much more serious a sudden decrease of aortic pressure might be if coronary vessels are sclerosed in addition.

There can be no doubt that the patient with great hypertension is confronted with certain risks, such as rup-

ture of blood vessels or decompensation of the heart. But physiological considerations suggest that in attempting to avoid these dangers the wise physician will consider carefully whether an even greater risk is not incurred through the use of drugs which lower systemic pressures generally.

BIBLIOGRAPHY

Arterial Elasticity and Pulse Velocity

Bazett, H. C. and Dryer, N. B.: Measurements of pulse wave velocity, Am. Jr. Physiol., 1922, lxiii, 94-116.

Bramwell, J. C.: Arterial elasticity in man, Quart. Jr. Med., 1924, xvii, 225-243.

Bramwell, J. C. and Hill, A. V.: The velocity of the pulse wave in man, Proc. Roy. Soc., 1922, xciii, Series B, 229-306. Velocity of transmission of pulse-wave and elasticity of arteries, Lancet, 1922, i, 891-892.

Bramwell, J. C., McDowall, R. J. S., and McSwiney, B. A.: The variation of the arterial elasticity with blood pressure in man, Proc. Roy. Soc., 1922-23, xciv, Series B, 450-454.

Bramwell, J. C., McDowall, R. J. S., and McSwiney, B. A.: The velocity of the pulse wave in man in relation to age as measured by the hot-wire sphygmograph, Heart, 1921-23, ix-x, 237-249.

Bramwell, J. C., Downing, A. C., and Hill, A. V.: The effect of blood pressure on the extensibility of the human artery, Heart, 1921-23, ix-x, 289-300.

Erlanger, J., and Hooker, D. R.: An experimental study of blood pressure and of pulse pressure in man, Johns Hopkins Hosp. Rep., 1904, xii, 145-378.

Frank, O.: Die Elastizität der Blutgefässe, Ztschr. f. Biol., 1920, lxxi-ii, 255-272; 1928, lxxxviii, 105-118.

Frank, O.: Das Altern der Arterien, Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in Münch., 1927, xxxvii, 23-32. (Abstract in Ber. ü. d. Gesamte Biol., Abt. b. Physiologie, 1927, xli, 234-235.)

Friberger, R.: Über die Pulswellengeschwindigkeit bei Arterien mit fühlbarer Wandverdickung, Deutsch. Arch. f. klin. Med., 1912, xcvii, 280-295.

Hemingway, A., McSwiney, B. A., and Allison, P. R.: Extensibility of human arteries, Quart. Jr. Med., 1928, xxi, 489-498.

Lyon, D. M., and Sands, J.: Studies in pulse wave velocity. IV. Effect of adrenalin on pulse wave velocity, Am. Jr. Physiol., 1924, lxxi, 534-542.

Laubry, C. H., Mougeot, A., et Giroux, R.: La vitesse de propagation de l'onde pulsatile artérielle, Arch. d. mal. du coeur, 1924, xiv, 49-70.
Hypotension artérielle, Arch. d. mal. du coeur, 1924, xiv, 97-129.

MacWilliam, Proc. Roy. Soc., 1902, lxx, 107.

Münzer, E.: Die Fortpflanzungsgeschwindigkeit der Pulswellen in gesunden und krankhaften, veränderten Blutgefässen, Verhandl. d. Kongresses f. inn. Med., 1912, xxix, 431-443.

Roy, C. S.: The elastic properties of the arterial wall, Jr. Physiol., 1880-1, iii, 125-129.

Sands, J.: Studies in pulse velocity; pulse wave velocity in pathological conditions, Am. Jr. Physiol., 1925, lxxi, 519-533.

Strasburger, J.: Über den Einfluss der Aortenelastizität auf das Verhältnis zwischen Pulsdruck und Schlagvolumen des Herzens, Deutsch. Arch. f. klin. Med., 1907, xci, 378-427.

Mechanisms Producing Peripheral Resistance Increase

Gager, L. T.: Hypertension, 1931, Williams and Wilkins Company, Baltimore.

Hering, H. E.: Arterieller Hochdruck und Arteriolen-Veränderung, Ztschr. f. Kreislaufforsch., 1930, xxii, 231-236.

Hochrein, M.: Habilitationsschrift, 1928, Vogel, Leipzig.

Koch, E., Mies, H., and Nordmann, M.: Arterieller Hochdruck durch Dauerausschaltung der Blutdruckzügler, Ztschr. f. Kreislaufforsch., 1927, xix, 585-600.

NORDMANN: Über Aortenveränderungen nach Dauerausschaltung der Blutdruckjügler, Münch. med. Wchnschr., 1928, lxxv, 1658.

REGNIERS, P.: Le sinus carotidien en clinique, Rev. belge sc. méd., 1930, ii, 601-622.

Experimental Hemodynamics and Cardiodynamics

FAHR, G.: Work of left ventricle in normal, hypertension and arterio-sclerosis, Proc. Soc. Exper. Biol. and Med., 1927, xxiv, 405-410.

FAHR, G., and DAVIS, J.: Effect of general systemic arteriosclerosis upon heart and systemic circulation, Ann. Int. Med., 1930, iv. 211-216.

FAHR, G., DAVIS, J. C., and SPITTLER, R.: Hemodynamics of arteriosclerosis; influence of elastic factor on circulation, Proc. Exper. Biol. and Med., 1929-30, xxvii, 325-327; Am. Jr. Physiol., 1931, xcvi, 426-438.

HOLMAN, E., and BECK, C. S.: The physiological response of the circulatory system to experimental alterations, Jr. Exper. Med., 1925, xlii, 661-692.

KATZ, L. N.: Observations on the external work of the isolated turtle heart, Am. Jr. Physiol., 1922, xcix, 579-597.

STARLING, E. H., and VISSCHER, M. B.: The regulation of the energy output of the heart, Jr. Physiol., 1926-27, lxii, 243-261.

WIGGERS, C. J.: Modern aspects of the circulation in health and disease, 1923, Lea and Febiger, Phil. and N. Y.
The pressure pulses in the cardiovascular system, 1928, Longmans, Green and Company, London.

WIGGERS, C. J. and KATZ, L. N.: Static and dynamic effort of heart during ejection, Am. Jr. Physiol., 1928, lxxxv, 229-250.

Physiology of Clinical Hypertension

BURWELL, C. S., and SMITH, N. C.: Output of heart in patient with abnormal blood pressures, Jr. Clin. Invest., 1929, vii, 1-10.

ERNST, C., and WEISS, R.: Über das zirkulatorische Minutenvolumen bei der Hypertonie, Ztschr. f. d. ges. exper. Med., 1929, lxvii, 126-138.

FEIL, H. S., and KATZ, L. N.: Clinical observations on the dynamics of ventricular systole. II. Hypertension, Arch. Int. Med., 1924, xxxiii, 321-329.

HOCHREIN, M.: Habilitationsschrift, 1928, Vogel, Leipzig.
Über den Kreislaufmechanismus bei der Hypertension, Arch. f. exper. Path. u. Pharmakol., 1928, cxxxiii-cxxxiv, 325-384.

LAUTER, S., und BAUMANN, H.: Über den Kreislauf bei Hochdruck, Arteriosklerose und Apoplexie, Ztschr. f. klin. Med., 1928, cix, 415-446.

WEISS, S., and ELLIS, L. B.: Quantitative aspects and dynamics of circulatory mechanism in arterial hypertension, Am Heart Jr., 1930, v, 448-468.

Essential (Primary) Hypertension: A Clinical and Morphological Study of 375 Cases*†

By Francis D. Murphy, M.S., M.D., F.A.C.P., John Grill, M.D., Benjamin Pessin, B.S., M.D., and Gail F. Moxon, A.B., M.D.,
Milwaukee, Wis.

THE variety of symptoms and vascular lesions associated with essential hypertension is so great that consecutive stages of the disorder may appear at times to be diseases of different kinds. Most cases of essential hypertension conform to the usually well recognized course of chronic hypertension which terminates, after years, in heart failure, cerebral hemorrhage, renal failure or some intercurrent infection. But there is a small group of cases, which, because of the peculiarities of the symptoms and vascular lesions, has been set aside by some observers in a separate class and designated "malignant" hypertension. Over the pathogenesis of the arteriolar lesions in this group, especially in the kidney, considerable controversy has arisen.

As early as 1910 Volhard and Fahr[1] differentiated the red granular kidney from the genuine contracted kidney leading to renal insufficiency. They[2] later clearly distinguished two forms of essential hypertension: (a) the benign form characterized by arteriosclerosis of the small renal arteries and (b) the malignant form or the combination form distinguished by the addition of an inflammatory factor to the kidney already damaged by arteriosclerosis. Although there has been objection to the use of the terms benign and malignant in connection with cases of hypertension, they have become so well established in the literature that it is difficult to discuss hypertension without referring to them. The division of cases of hypertension into benign and malignant forms is convenient. But it must be recognized that benign cases may end fatally in uremia; the benign case may become transformed into the malignant one; there may be intermediate cases having features of the benign type with a few of the characteristics of the malignant form; and finally that there may be degrees of intensity of the symptoms and vascular lesions within the malignant group.

In this report an analysis is presented of the clinical and postmortem

*From the Departments of Medicine and Pathology of Marquette University School of Medicine, and the Medical Clinics of the Milwaukee County Hospital, Milwaukee, Wis.

†Presented at the San Francisco meeting of the American College of Physicians, April 6, 1932.

data obtained from a study of 375 cases of primary (essential) hypertension. An attempt is made to show that the varieties of clinical and morphological changes observed are manifestations of the different stages of one process. In order to obviate the impression that the cases with an intense and rapid course may be considered as a separate condition, and to emphasize the unity of the clinical and morphological features, all cases are divided into three groups corresponding to three consecutive stages of the disease. This grouping is unimportant except that it is of immediate convenience. Cases of early hypertension in which symptoms appear to be independent of the vascular lesions are placed in group 1; this may be called the functional stage. In group 2 are the cases in which hypertension is associated with definite arteriosclerosis slowly progressing to the breakdown of essential organs; this may be designated the arteriosclerotic stage. And finally, in group 3, are the cases of so-called malignant hypertension. Corresponding to the stormy clinical course are the necrotic lesions in the arterioles of the kidney and other organs; hence the term arteriolonecrotic stage may be appropriate for this group.

Material Studied

For the purpose of this report cases were included in which there was a persistent systolic blood pressure of 160 mm. of mercury or above, and a diastolic pressure of above 100 mm. of

Fig. 1. (Group 1). Normal glomeruli and arteries seen in group 1.

mercury. Cases of glomerular nephritis, toxemia of pregnancy, hyperthyroidism and aortic regurgitation were excluded, as well as any other case in which the cause of the hypertension was apparent.

Hypertension, without clinical evidences of arteriosclerosis other than those seen in normal people, was the chief feature of cases in group 1. There were no symptoms or signs ordinarily present in cardio-vascular-renal disease. Symptomatically a vasomotor derangement of the type often seen in neurasthenia was the essential change. Frequently there were no symptoms. Patients died of causes independent of cardio-vascular-renal changes; an accident, an operation, or an intercurrent infection was the chief cause of death. There were 43 cases in group 1. In group 2 the cases are recognized as those having arteriosclerosis of peripheral as well as internal arteries. This group represents a stage of slow progression and the symptoms are those produced by arteriosclerotic narrowing of the lumina of arteries leading to ischemia and slow fibrosis of internal organs. Heart failure, cerebral accident, renal failure and thrombosis may appear in this stage. There were 303 cases in group 2. The remaining 29 cases were placed in group 3. Clinically the patients of the last group had the following distinctive features: a) persistent excessive hypertension; b) violent headaches; c) rapid progressively downward course; d) sudden loss of weight and strength; e) typical retinal changes; f) a course resistant to treatment; and g) a termination with a functional breakdown of some essential organ, usually the kidney or the heart. Histologically there was an advanced severe diffuse arteriosclerosis with necrotic lesions of the arterioles of various organs. A detailed analysis of the clinical and histological features of 12 of the 29 cases included in group 3 was reported previously by Murphy and Grill.[3]

Analysis of Clinical Data

The causes of death in this series as well as the number and percentage of each are arranged in five groups as shown in table 1. Heart disease caused death in 188, or 50 per cent of all cases. It is seen that 171, or

Table 1

Causes of Death in 375 Autopsied Cases of Essential Hypertension

	Group I		Group II		Group III		Total	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
1. Heart disease	10	23.3	171	56.4	7	24.1	188	50.0
2. Renal failure	0	0	23	7.6	16	55.2	39	10.4
3. Apoplexy or thrombosis and embolism	0	0	45	14.9	5	17.2	50	13.4
4. Infections	12	27.9	40	13.2	1	3.5	53	14.2
5. Miscellaneous	21	48.8	24	7.9	0	0	45	12.0
Total	43	100.0	303	100.0	29	100.0	375	100.0

56.4 per cent of cases, in group 2 died of heart disease while in group 3 only 7, or 24.1 per cent, had heart failure. Ten patients, or 23.3 per cent, of group 1 died of heart disease but usually of a type produced by infections and not hypertension. In sharp contrast to the percentage of deaths caused by heart disease was the low mortality rate from renal failure. Thirty-nine only, or 10.4 per cent, died from renal failure. Of these 23, or 7.6 per cent, occurred among cases of group 2; 16, or 55.2 per cent, among those of group 3. In group 2 uremia followed a slowly progressing renal failure, but in group 3 uremia developed suddenly and caused early and rapid death. It was unexpected to find that only 45, or 14.9 per cent, of the patients in group 2 died of cerebral hemorrhage or thrombosis, while in group 3 five deaths from apoplexy, or 17.2 per cent, were not exceptional. Of the infections which caused death in 53 cases, or 14.2 per cent, pneumonia was the most prominent. Erysipelas and gangrene of the feet occasionally occurred.

The ages of the patients ranged from 9 to 100 years. They are arranged according to decades and the number and per cent in each group are given in table 2. In group 3 (malignant), 62.3 per cent of the individuals were under 50 years of age; while in groups 1 and 2 (benign), 16.3 per cent were under 50 years of age. In order to emphasize this interesting comparison the age incidence was arranged as shown in table 3. The occurrence of so many patients of advanced years may be explained by the fact that many of the patients were inmates of a county infirmary.

Throughout the three stages there were two unifying clinical factors, hypertension and left ventricular hypertrophy. The length of time elapsing between the onset of hypertension and the occurrence of other symptoms was unknown in most cases. However, in some cases it is known that as short a time as one year, and in other cases as long as 15 years, elapsed before the usual symptoms developed. The degree of hypertension in groups 1 and 2 varied considerably, fluctuating in some cases between 150 mm. and 300 mm. of mercury systolic, and from 100 mm. to 160 mm. of mercury dias-

TABLE 2

AGE INCIDENCE IN 375 AUTOPSIED CASES OF ESSENTIAL HYPERTENSION

AGE	GROUP I		GROUP II		GROUP III		TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO	PER CENT	NO.	PER CENT
10- 20	0	0	0	0	3	10.4	3	0.8
21- 40	9	21.0	8	2.64	7	24.1	24	6.4
41- 60	23	53.5	65	21.5	15	51.7	103	27.3
61- 80	10	23.2	166	54.8	4	13.8	180	48.1
81-100	0	0	35	11.5	0	0	35	9.4
UNKNOWN	1	2.3	29	9.6	0	0	30	8.0
TOTAL	43	100.0	303	100.0	29	100.0	375	100.0

TABLE 3

A COMPARISON OF AGES OF PATIENTS IN GROUPS 1, 2, AND 3

AGE	(BENIGN) GROUPS 1 AND 2		(MALIGNANT) GROUP 3	
0-10	0		1	
11-20	1		2	
21-30	3	16.3%	2	62.3%
31-40	12		6	
41-50	36		7	
51-60	56		7	
61-70	100	83.6%	4	37.7%
71-80	80		0	
81-100	30		0	
TOTAL	318		29	

tolic. In group 3 this changeableness was less noticeable. The accompanying symptoms appeared to bear no relation to the height of the blood pressure in any group. In group 2 a few patients were observed who showed systolic pressures above 200 mm. of mercury and independent of treatment had normal pressures with no heart failure within a period of one year. Of the 303 cases in group 2, 32 or 10.5 per cent had no hypertension during the last period of observation preceding death. Previous records in some of the cases proved hypertension to have been present on former observations. In other cases, evidences such as cardiac hypertrophy, retinal and peripheral arteriosclerosis, as well as arteriosclerosis of the smaller arteries in the kidney were taken as proof of a pre-existing hypertension. Obviously the blood pressure dropped in many cases of coronary disease and myocardial failure.

Left ventricular hypertrophy was present at autopsy in 263, or 79.4 per cent, of all cases; there was no record in 44 and in 68 cases no enlargement was present. Of the 263 cases of proved left ventricular hypertrophy, only 182 were recognized clinically, indicating a considerable disparity between the clinical and postmortem figures. The two chief clinical manifestations of heart disease were angina pectoris and the syndrome of left ventricular failure. The frequency of angina pectoris was difficult to determine because patients were frequently unable to distinguish between pain in the cardiac area and other sensations often produced by left-sided heart failure, such as constriction, heaviness, distension, and suffocation in the sternal region. It was estimated that 42, or 11.2 per cent, of the 375 patients had angina pectoris. Pain in the heart area was the first symptom of heart disease in approximately 18, or 5 per cent, of all patients having heart failure. The syndrome of left ventricular failure was the outstanding feature. Of the 188 patients dying of heart disease it was the first evidence of any disorder noted by the patient in 105, or 55.8 per cent. This classical syndrome developed in every case of heart failure from hypertension. It was characterized by paroxysmal dyspnea usually worse at night, palpitation of the heart, and a sense of distress in the heart area. Dyspnea, usually nocturnal at first, was the earliest symp-

tom of heart failure in most cases although attacks of dyspnea varied in time and duration; as a rule, they persisted for about twenty minutes in the earlier stages and then subsided only to return about the same time the following night. Frequently patients worked during the day without experiencing recurrent attacks. After some weeks or at times months, attacks came during the day and recurred so frequently that the patient was confined to bed. With the onset of this type of dyspnea, the outlook for the patient was distinctly bad; a few patients, however, recovered and lived only to die of heart failure or apoplexy in later years. Palpitation, although frequently present, was the first symptom in only a few cases.

Murmurs were most frequently heard at the mitral area, being recorded in 85 cases, or 22.6 per cent of all cases. Aortic systolic murmurs were less common, being noted in 52, or 13.8 per cent of cases. A soft diastolic aortic murmur transmitted down the left sternal border was occasionally found. Of greater importance than murmurs was the frequent presence of a gallop rhythm. It was noted in 95, or 50.5 per cent, of the 188 cases of heart failure. Usually the onset of gallop rhythm indicated a progressive left ventricular failure. A few exceptions to this rule were observed.

FIG. 2. (Group 2). Focal thickening of the capillary basement membrane with mild arteriosclerosis. Azo-carmine stain.

Electrocardiographic examinations revealed a variety of changes. The most common were left ventricular preponderance and evidences of left bundle branch block; many were normal.

Although an arteriosclerotic contracted kidney was commonly found at autopsy, uremia was a rare complication, occurring in only 39, or 10.4 per cent, of all cases.

Clinically the following renal functional tests were used routinely in all cases: (a) phenolsulphonphthalein test, (b) urea concentration test of McLean, (c) dilution and concentration tests of Volhard, (d) blood nitrogen estimations weekly, (e) the urea clearance test was used to some extent during the past two years and was found to be the most satisfactory one in giving information of early renal failure. In group 3 the kidney destruction from the necrotic and thrombotic complications of the arteriosclerosis was associated with sudden and early uremia; while in group 2 the ischemic atrophy of the kidney was a slower process taking months and years completely to render the kidneys insufficient. Albuminuria was a constant feature of cases in both groups having renal failure. There was, however, a difference in the response to treatment of the renal failure in the two groups; renal failure in group 3 was decidedly resistant to treatment while that in group 2 frequently appeared to be benefited by treatment. Frequently albumin was found independent of casts, red blood cells and pus cells. In such cases the albuminuria was assumed to be caused by renal congestion from a failing heart. The presence of small quantities of albumin associated with many red cells and pus cells was considered to be evidence of small infarcts due to arteriosclerotic occlusion of smaller arteries. Heavy albuminuria with casts, red cells and pus cells was found with renal failure in both groups 2 and 3. Extrarenal factors, such as heart failure and infections added to kidneys already damaged by arteriosclerosis, occasionally caused renal failure. Edema of the nephritic type did not occur in this series. There was no hypercholesterolemia present and doubly refracting lipoids were not found in the urine of patients suffering from edema. The albumin and globulin content of the blood was always normal in cases in which estimations were done. Edema, when present, was of the cardiac variety. Although pallor of the skin was noticeable in many cases, anemia was infrequent except in cases of renal failure when it was observed in some but not all cases.

Apoplexy was the cause of death in 50, or 13.4 per cent, of the cases. Hemorrhage in other parts of the body was occasionally observed. There were two cases of renal hemorrhage; one case had hemoptysis and autopsy revealed no pulmonary tuberculosis or any disease aside from arteriosclerosis. Hematemesis was observed once in this series. Epistaxis was more frequent. Vascular crises producing transient hemiplegia or aphasia with monoplegia were observed four times. In a few cases in group 3 there were periodic attacks of abdominal cramps and of severe headache. Such attacks were believed to be caused by vascular crises involving visceral arteries of the ab-

domen and of the brain respectively. These periodic attacks remained for periods varying from several hours to several days. There were two patients belonging to group 3 who developed hemorrhages into the skin resembling purpura hemorrhagica. The lesions varied in size from several millimeters to large blotches of several centimeters in diameter. The disease in both instances progressed rapidly to a fatal termination.

Retinal Changes

Recent work done in this country chiefly by O'Hare and Walker,[4] Keith, Wagener and Kernohan[5], Fishberg and Oppenheimer,[6] and Wagener,[7] has established the relationship between the various stages of hypertension and the changes in the arterioles of the retina. In accordance with other observers we have found the vascular changes in the retina one of the best indicators of the degree of vascular changes throughout the body. For the purpose of prognosis the retinal lesions in group 3 are of considerable importance.

In the cases of early essential hypertension (group 1) the retinal examinations revealed no abnormalities. In cases of longer duration, evidences of arteriosclerosis were usually present. Narrowing of the arterioles with increase of the light-reflex of the arteries, tortuosity of the arteries and arteriovenous compression were the usual features. Occasionally, there were small hemorrhages along the course of some vessels and at times white patches were seen produced probably by an old healed hemorrhagic area. The disks in this group were clear and edema of the retina was mild. By observing these eye changes from time to time the rate of progress of arterioslerosis may be determined. Usually the retinal arteriosclerosis in group 2 was a slowly changing process corresponding in general with the vascular changes in the kidney and in other organs of the body. The lack of destructive changes in the disks was in sharp contrast with the lesions seen in the more advanced cases of group 3 (malignant). The changes in the eye grounds in group 3 were more characteristic than in group 2. Obviously, since the vascular lesions of groups 2 and 3 are only different stages of one process, cases were seen in which the changes in the eye were of the transitional form corresponding to the type termed by Wagener[7] retinitis of severe benign hypertension. Lesions of the fundi were always found in group 3 and were characterized by papilledema, hyperemia of the disks, and constriction of the arterioles leading to the appearance of thin white lines buried in the retinal edema. Hemorrhages along the course of the arteries were frequently found. White patches were seen which corresponded to what has been designated "cotton wool" patches. These patches seemed fresher and had irregular borders that appeared to merge with the generalized edema of the retina. They lacked the clearcut glistening features of those white patches seen in the cases of group 2. In three cases in group 3 a previous diagnosis of brain tumor was made upon the changes of the eye grounds. In two of our cases in group 3, the characteristic lesions in the fundus were present before any evidence of renal damage occurred. Al-

buminuria and renal failure developed within the first few months of observation. One case in group 3 was noted in which the advanced changes in the eye grounds were absent. There was no abnormality except a mild arteriosclerosis of the retinal arteries and yet the patient died of uremia. Histologically the kidneys showed the typical arteriolonecrotic lesions seen in malignant nephrosclerosis of Fahr. When the typical retinal changes are found in the absence of renal and heart failure it is fairly certain that breakdown of the organism will follow within a period of several months. That onset of renal failure does not influence markedly the retinal picture is concluded from a study of our cases of renal arteriosclerosis with gradual renal failure in group 2. Of the 23 cases of ischemic atrophy of the kidney leading to renal insufficiency, eight were examined ophthalmoscopically. No changes were observed other than a simple arteriosclerosis. We found that the retinal vascular changes are a fair index of the lesions progressing in other organs of the body. For the purpose of exact diagnosis and prognosis ophthalmoscopy is of no little importance.

Analysis of Pathological Data

Postmortem examinations were made in all the cases. All sections were studied with hematoxylin and eosin; Van Gieson's and Weigert elastic tissue stains and Sudan III. Selected cases were studied with modified Heidenhain-Mallory stain. When fat was present polariscopic examinations were made for doubly refracting lipoids. Corresponding to the clinical groups representing successive stages of the disease, three stages of arteriosclerosis were recognized. Mild arteriosclerosis involving chiefly larger and medium sized arteries of organs such as the kidney, liver and spleen was the main feature of group 1. A more advanced arteriosclerosis of the smaller as well as the larger arteries of kidneys and other organs characterized group 2. The essential change in group 3 (malignant) was an intense diffuse arteriosclerosis extending into the smallest arteries and arterioles and producing at times an arteriolonecrosis.

As shown in table 4, cardiac hyper-

Table 4

Heart Weights in 375 Cases of Essential Hypertension

Heart weights	Group 1		Group 2		Group 3		Total	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Normal weight	18	41.85	50	16.5	0	0	68	18.13
400- 600 gms.	14	32.55	151	49.84	14	48.27	179	47.74
600- 800 gms.	7	16.3	51	16.83	9	31.03	67	17.87
800-1000 gms.	0	0	14	4.62	3	10.35	17	4.53
Not recorded	4	9.3	37	12.21	3	10.35	44	11.73
Total	43	100.00	303	100.00	29	100.00	375	100.00

trophy was found in 263, or 79.4 per cent, of 331 hearts examined; in 44 no record was made. Slight left ventricular hypertrophy was noted in group 1; 21 of 39 hearts were above normal weight. Of 266 in group 2, 216, or 81 per cent, were hypertrophied, while in group 3 hypertrophy was present in every case recorded. Coronary disease, characterized grossly by occlusion of a large branch of the artery from thrombosis or a decided narrowing due to arteriosclerosis was recorded in 44, or 25.7 per cent, of 171 cases examined in group 2. In these cases myocardial infarcts or scars and diffuse fibrosis of the heart muscle were present. Occasionally a diffuse fibrosis and scars were present when the coronary disease seemed insufficient to cause any trouble. In 4 cases the left ventricle was considerably hypertrophied and dilated and little or no fibrosis or coronary disease was found. Death was due in each case to left ventricular failure. In no case in group 3 was there macroscopic evidence of complete coronary occlusion, although coronary sclerosis with narrowing was always found. Arteriosclerotic lesions of the aortic valves leading to deformities and insufficiency were occasionally observed. Less often, the mitral valve was involved in the arteriosclerotic

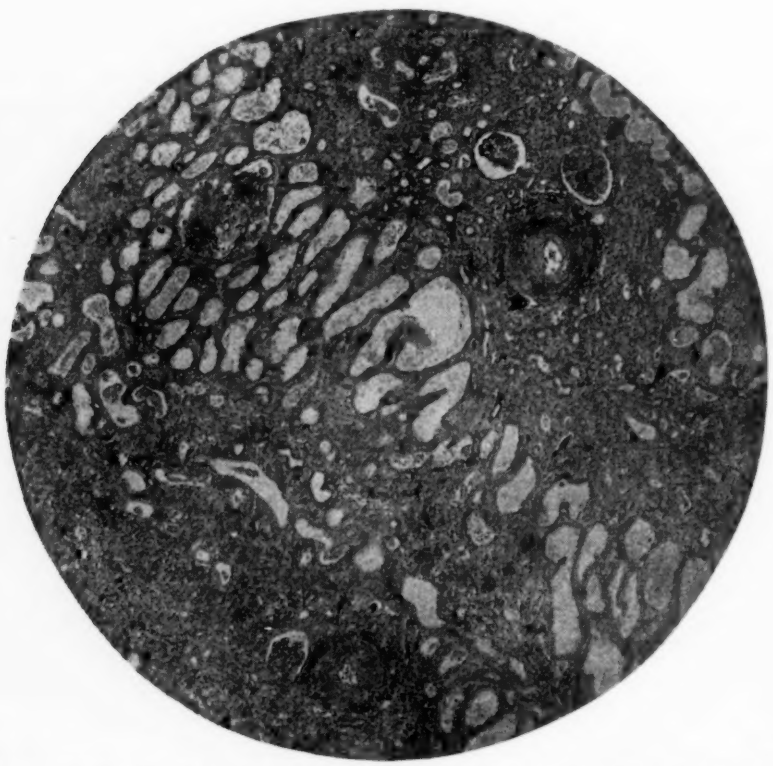


FIG. 3. (Group 3). Section showing the increase in the stroma, the dilated tubules, the sparsity of the glomeruli, and the extensive arteriosclerosis of the smallest arteries.

process. The arterioles of the myocardium were usually normal.

The size and appearance of the kidneys were decidedly variable. Some kidneys were shrunken and granular; others were large and smooth. Microscopically arteriosclerosis of the small arteries of the kidney was constantly found. In some cases it was widespread; in others, it had a focal distribution. Variations in size, color and surface markings did not conform to any stage of the disease. Kidney weights were available in 267 cases. The average weight in 33 cases of group 1 was 181.5 gm.; of the right, 176 gm., and of the left, 187 gm. In group 2, the average weight of kidneys in 205 cases was 133.5 gms.; of the right, 129, and of the left, 138 gm. The largest kidney weighed 280 and the smallest 90 gms. In the 29 cases of group 3 the average weight was 115 gms.; of the right kidney, 112, and of the left, 116 gms. The smallest kidney weighed 29 gms.; the largest, 255 gms. In one case there was a congenital absence of the left kidney; the right weighed 255 gms.

Kidneys in group 1 were always either normal in size or larger than usual and the surface was smooth. Evidences of arteriosclerosis were confined to the larger branches, and yellowish streaks in the intima due to lipoid deposits were frequently the only sign of disease. Grossly the kidneys in group 2 were of the shrunken granular type. The degree of contraction and granulation varied. Scattered scars due to healed infarcts were occasionally seen on the surface of an otherwise normal appearing kidney. The cortex of the kidneys in both groups 2 and 3 was narrowed, and especially in group 2, accumulation of fat appeared in the renal pelvis. Kidneys of the contracted granular type were usually present in group 3. Occasionally they were larger than normal with a smooth surface or of normal size without granulation. Extensive subcortical hemorrhages were present in all but 5 cases. Small hemorrhages in the mucosa of the pelvis were constantly found; and in several cases there were blood clots with evidences of larger hemorrhages from the kidney.

Microscopically the changes in group 1 were few and were substantially the same as those in non-hypertensive individuals of the same age. The arterioles and the smaller portions of the interlobular arteries were normal. Occasionally there were areas showing arteriosclerosis of the medium-sized arteries along with foci of hyalinized and fibrosed glomeruli. Such lesions were the same as those found in the later stages, except that they were so few in number that they may be looked upon as normal. Concerning the size of the glomeruli there was no constancy. Most glomeruli were of normal size, some were hypertrophic, and a few were atrophic. The tufts undergoing atrophy showed various grades of hyaline and fatty degeneration and fibrosis. The glomeruli in many cases were further studied with the Mallory-Heidenhain azo-carmine stain, as suggested by McGregor.[8] All of the cases in group 3 and 141 cases in groups 1 and 2 were examined with this stain. In group 1 and in some cases of group 2 representing the earlier stages of arteriosclerosis, focal thickening of the

glomerular basement membrane was observed. Thickening and wrinkling of the glomerular basement membrane was noted in some cases where the smallest arteries and arterioles were intact. In more pronounced cases of contracted kidney these changes in the basement membrane were widespread and the glomeruli were more diffusely involved. Although thickening of the glomerular basement membrane was present with contraction of the renal corpuscle in some form in all cases of hypertension, such changes cannot be considered specific for cases of hypertension only, as identical changes in the basement membrane were observed in cases known to have had no hypertension. Similar changes were easy to demonstrate in kidneys of older people where the afferent arterioles as well as smaller arteries were free from arteriosclerotic changes.

In group 2 the arteriosclerosis had advanced to such extent that functional derangement of some internal organ followed ischemia. Of the lesions present in all organs, those in the kidney were found to be the most accurate index of the progress of arteriosclerosis. The predominant lesion was an arteriosclerosis of the larger and medium-sized arteries. In some cases, however, there was an extension of the arteriosclerotic process into the smaller and smallest branches of the interlobular artery. Occasionally the arterioles were involved. However, such changes were distinctly focal in distribution and frequently led to scattered renal scars. Patches of destroyed tufts were seen with corresponding tubules which showed round cell infiltration and in places advanced fibrosis with scarring. There were many glomeruli which appeared almost twice normal size; at the same time many were shriveled and atrophic. The number of normal glomeruli depended upon the extensiveness of the arteriosclerosis. Capsular thickening was found varying from a slight proliferation of connective tissue to a thick ring of scar tissue which seemed to obliterate the capillary tuft. Associated with this were areas of interstitial fibrosis, round cell infiltration and peri-glomerular fibrosis. Hyaline and fatty degeneration of afferent arterioles with extension of the degeneration into the glomeruli were frequently seen. A distinct feature was the diffuse thickening of the capillary basement membrane. This thickening, in contrast to the earlier stage seen in group 1, was almost universal in many cases. It is obvious that within group 2 there may be a variety of histological changes depending mostly upon the extent and severity of the arteriosclerotic process. Although in groups 1 and 2 the essential histological lesion is an arteriosclerosis, the chief contrasting feature is the degree of involvement of the various organs. In group 2 the arteriosclerotic process is no longer limited to larger and medium sized arteries but in the kidney the process extends at times down to the finest vessels.

The vascular lesions of the kidney described in group 3 (malignant) have some distinguishing features which have led to their separation from the simple arteriosclerotic renal lesions under the term malignant renal sclerosis. The foudroyant destructive lesions of the kidney in group 3 were in sharp

contrast with the benign sclerosis just described. Although the clinical picture in this group was fairly uniform, the histological lesions showed various degrees of degenerative lesions. In some cases necrosis of arterioles with thrombosis of corresponding capillary loops was a frequent change, and in others an extensive severe arteriosclerosis with little or no necrosis dominated the picture. An analysis of the cases in this group suggests that the typical clinical syndrome may precede the onset of necrosis of renal arterioles. Furthermore heart failure, apoplexy, or some other complication may terminate the patient's life before renal necrosis occurs. The renal artery was arteriosclerotic in all cases. The lumina of the arcuate and interlobular arteries were reduced in diameter in all instances due to arteriosclerosis. In all cases the cortical stroma was increased but the density varied. Focal infiltration with lymphocytes, plasma cells and occasionally polymorphonuclear leucocytes was a feature of all cases. Alteration of the tubules was constantly present. Areas of dilated tubules with low atrophic epithelial cells were adjacent to islands of compressed atrophic tubules surrounded by increased stroma. Fatty and granular degeneration of the epithelial

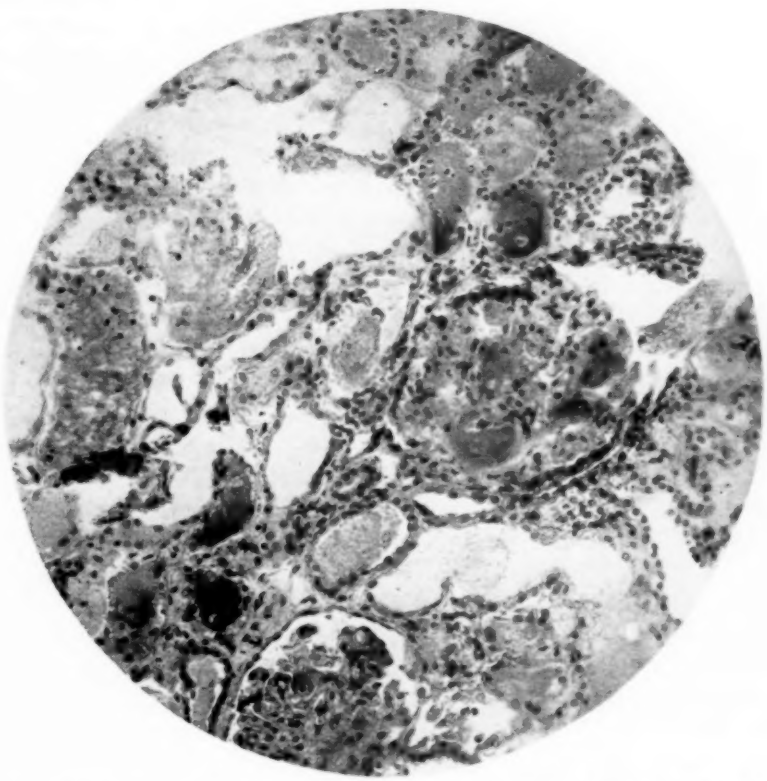


FIG. 4. (Group 3). Arteriolonecrosis with glomerulus illustrating necrosis in capillary loops.

cells of the tubules with necrosis in some portions was frequently observed.

Damage of the glomeruli was a constant change but the extent of damage varied. Many glomeruli were larger than normal and the capillary loops were normally filled with blood. Others were smaller and more cellular than normal and the loops were bloodless; and again at times the capillary loops appeared to be gorged with red blood cells. The increase in cellularity was caused by an increase in the endothelial and epithelial cells. In some places the capillary loops were adherent to the thickened Bowman's capsules. Thickening of the capsule with desquamation and proliferation of the glomerular and capsular epithelium produced crescents in some glomeruli. In other glomeruli only portions of the loops were involved leaving the remaining part of the tuft normal. Many glomeruli were reduced in size, and fatty and hyaline degeneration of the walls of the loops led to a collapse of the tuft. Hyaline droplet degeneration of the epithelium was frequently demonstrated. There was a widespread and extensive fatty degeneration of the epithelium and capillary endothelium of the glomeruli. The capillary basement membrane of the glomeruli was universally thickened and wrinkled as shown with the aniline-blue stain. In cases where death was caused by apoplexy or heart failure before uremia developed, the glomeruli were usually not so greatly damaged.

The most characteristic microscopic feature was a severe arteriosclerosis attacking the smaller and smallest arteries and arterioles of the kidneys. The chief distinction was the diffuseness of this process. Elastic hyperplastic thickening of the arteries was present with excessive connective tissue proliferation of the intima of the smaller and smallest arteries. Fatty and hyaline degeneration of the arterioles, and especially the afferent glomerular arterioles, was an outstanding feature. In places fatty and hyaline degeneration occurred with necrosis of the arteriolar wall. In corresponding glomerular loops there was necrosis. Hemorrhagic infiltration of the necrosed arteriolar wall and of the capillary loops was a characteristic feature. The amount of necrosis, however, bore no relation to the degree of renal insufficiency; for in some cases of uremia, necrotic lesions were few and in others with intact function, necroses were numerous. More important was the diffuse intense arteriosclerosis leading to narrowing and obliteration of the lumina of the smallest arteries and arterioles with subsequent ischemia and degenerative changes in the glomeruli. There were degrees of arteriolar destruction depending upon the extent and severity of the necrotic lesions. In some cases necrosis of the arterioles was scarcely found, while in others it was widespread and severe. In one case with widespread arteriolar necrosis and many glomerular infarctions there were areas of perivascular and periglomerular leucocytic infiltration. Aside from this case no such leucocytic infiltration was observed in this series. Scattered throughout the cortex, in many cases, however, nests of leucocytes were observed.

Concerning the changes in the

media of renal arterioles, medial hypertrophy was found occasionally; usually there was atrophy of the media, and at times thickening was due to an increase of connective tissue in the media. Muscular hypertrophy was not a constant nor essential change in this group.

Histological studies were made of other organs including the spleen, lung, pancreas, and liver. In the spleen, liver and pancreas the vascular lesions paralleled those of the kidney quite uniformly. Arteriosclerosis of the smaller and smallest arteries leading to narrowing of the lumina was the chief change. Necrotic lesions were observed outside of the kidney and the eye in only two cases in group 3. In two cases a few necrotic arterioles were seen in the spleen. Pulmonary arteriosclerosis of the smallest arteries and arterioles was a rarity. In three cases there was narrowing of the arteries due to arteriosclerosis.

The arterioles of the skeletal muscle were examined in all cases of group 3 and in 124 cases of groups 1 and 2. The pectoralis major was the muscle usually examined. Hypertrophy of the media of the arterioles was constantly found in group 3. The degree of hypertrophy varied. In some cases it was so decided that the lumen of the vessel was almost closed; in others hypertrophy was slight. Moderate to advanced hypertrophy of the media of arterioles was also observed in 57 cases of group 2. Occasionally proliferation of the intima was observed in these cases.

Microscopic examination of the eye was made in two cases. The walls of the central arteries were thickened, and the lumina of the branches, especially the arterioles, were decidedly narrowed and occasionally totally obliterated. The choroidal arterioles were variously altered; areas of fatty degeneration and of necroses were seen. In places there was a mild leucocytic infiltration of the necrotic area. The retina was edematous and many hemorrhages were seen especially in the posterior part. No degenerative changes were seen in the arterioles of the extrinsic muscles; but the media was hypertrophied. The optic nerve was edematous and there was an inflammatory exudate composed of lymphocytes and plasma cells.

Discussion

The relationship of the three groups of cases of essential hypertension described here is shown by the presence of such unifying factors as hypertension, cardiac hypertrophy and arteriosclerosis, especially of the renal arteries and arterioles. Clinically and histologically the wide variety of symptoms and lesions encountered was dependent upon several factors. Chief among them was the location of the arteriosclerotic process leading to narrowing and frequently obliteration of the lumina of arteries followed by ischemia and failure of essential organs. In addition to the degree of intensity and extent of the arteriosclerosis, the speed of development of the arteriosclerotic lesions played an important part in determining the changes described. There appeared to be no constant relationship between the height of the blood pressure and the rate of progress or extensiveness of the arteriosclerosis. In some cases

there were no symptoms in the presence of extraordinarily high pressures over a period of years. Undoubtedly hypertension is an important influence in the production of arteriosclerosis, yet the inherent quality of the arteries themselves, and especially their ability to withstand strain, seems to be a more important factor. Since this paper deals only with fatal cases, obviously the study of group 1 is incomplete. Death occurred independently of the hypertension and associated vascular disorders. Ill-defined complaints or a total absence of symptoms characterized this group clinically. Histologically arteriosclerotic changes were few and were no more extensive than those seen in non-hypertensive individuals of the same age. No case was observed in which there was no renal arteriosclerosis; but in some cases it was limited to the larger and medium sized arteries. In the succeeding stages smaller and smallest arteries were damaged. The vagueness of the symptoms in early hypertension has been emphasized by Allbutt[9] and Mahomed.[10] Moschcowitz[11], too, pointed out the significance of the psychic makeup of individuals with essential hypertension. More recently Ayman and Pratt[12], Davis[13], Riseman and Weiss[14], and Rolleston[15] have reported

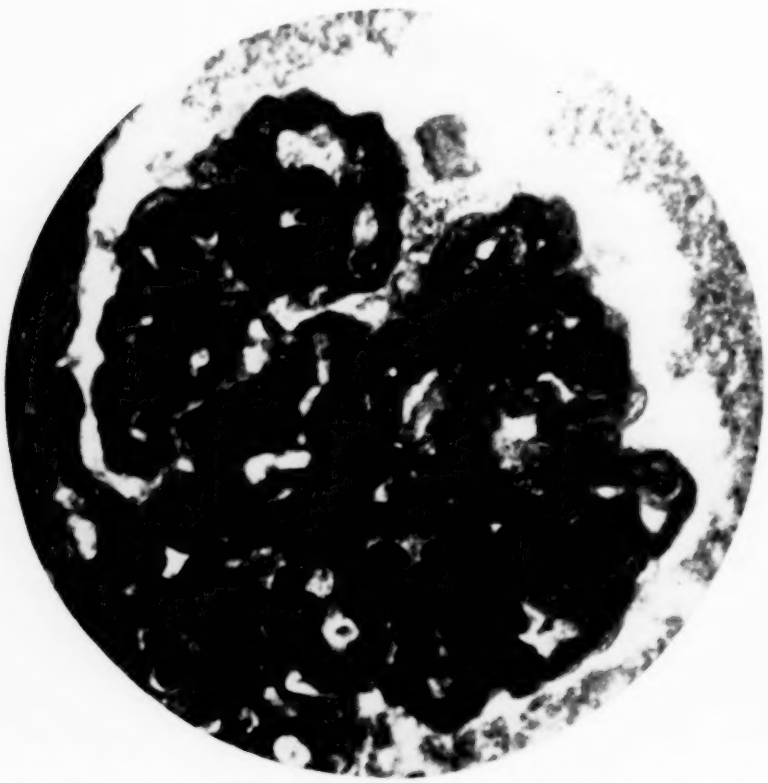


FIG. 5. (Group 3). A glomerulus showing the decided thickening and wrinkling of the capillary basement membrane, typical of glomeruli in group 3. Azo-carmine stain.

upon the symptomatology of many cases studied in the early stages. All of these investigators observed a parallelism between the early symptoms of essential hypertension and psychic states as seen in psychoneurotics. As emphasized by Fishberg[16], it is unusual to have a case of essential hypertension come to autopsy before hypertension has done any damage to renal arteries. He did, however, study two such cases.

Apoplexy, heart failure and renal failure were the chief complications observed in groups 2 and 3. As shown in Table 1, apoplexy was the cause of death in 50, or 13.4 per cent of cases. These figures are at variance with those of Herxheimer and Schulz[17] who reported that 179, or 44 per cent, of 403 cases had apoplexy. Bell and Clawson[18] found apoplexy in 81, or 19 per cent, of 420 cases. The low figures in our series may be explained by the fact that we included only the primary cause of death in the analysis. For illustration, a patient may have had a cerebral hemorrhage but may have died of uremia. A comparison of the analyses of the data on the heart in groups 2 and 3 reveals that coronary thrombosis or occlusion was an important cause of death in group 2, while it was unimportant in group 3. Of 171 hearts examined at autopsy in group 2, 44, or 25.7 per cent, had coronary occlusion of sufficient extent to damage the heart and cause heart failure, or a coronary thrombosis with a cardiac infarction. Obviously coronary arteriosclerosis was more common than these figures suggest, but only the cases are included in which the coronary disease was advanced enough to produce definite heart disease and failure. Recently Shapiro[19] reported causes of death in 171 cases of nephrosclerosis. In 16 cases (9 per cent) the cause of death was coronary accident. Of 394 cases of essential hypertension studied at autopsy by Herxheimer and Schulz[17] cardiac hypertrophy was present in 384 cases, or 97.5 per cent. Bell and Clawson[18] reported heart failure as the cause of death in 187 of 420 cases, or 44.5 per cent. If they included the coronary group, it was stated that 254 deaths, or 60.4 per cent, occurred from heart failure. In the present study we noted that 263, or 79.4 per cent, of 331 cases had cardiac hypertrophy.

In cases of renal arteriosclerosis Russell[20] found no evidence of renal impairment apart from the occasional excretion of a trace of albumin; all abnormalities in the tests for renal efficiency, complicated by heart failure, she believes, were such as known to be caused by heart failure. In our 23 cases of renal failure, heart failure as an important influence in the development of renal insufficiency was excluded. Patients with a combination of heart failure and renal failure were placed in the heart failure class. That a diminished renal function may occur ultimately in benign slowly progressive forms of renal arteriosclerosis is indicated by three cases reported by Van Slyke, and others[21]. The occurrence of renal failure in the course of hypertension with renal arteriosclerosis does not indicate that the case belongs to the malignant group any more than does the onset of cardiac failure or cerebral hemorrhage. As a consequence of hypertension and arteriosclerosis the lumina of the renal

arteries and arterioles often became so narrowed that an ischemic atrophy of the kidneys followed. In sharp contrast to the cases in group 3, the process in group 2 appears to develop slowly. Histologically no necrosis is seen, but a generalized arteriosclerosis of the larger and medium sized arteries is present with a focal arteriosclerosis of the smallest arteries and arterioles. The amount of fatty and hyaline degeneration and advanced arteriosclerosis is never so extensive as in group 3. Occasionally this benign process gradually leads to almost complete fibrosis of a sufficient number of the glomeruli to produce renal failure. We observed 23 such cases, or 7.6 per cent, in group 2. Owing to the slowness of progress of the arteriosclerotic process in group 2, patients lived longer free from complications than those in group 3. Consequently there was a decided contrast in the age incidence of the two groups as shown in table 3. Most cases of essential hypertension never progress into group 3 (malignant type); but they end fatally from some

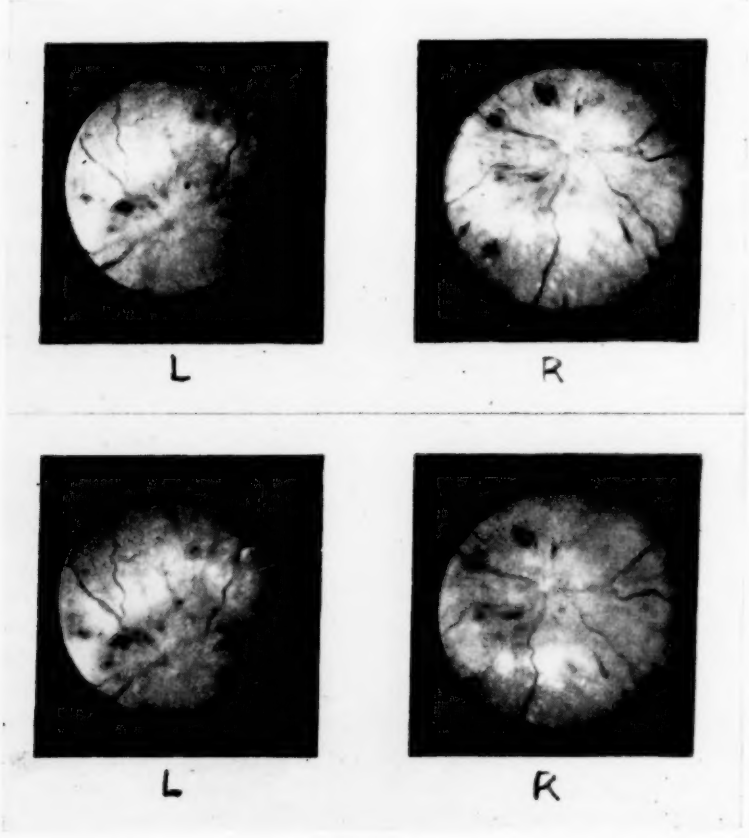


FIG. 6. (Group 3). A photograph of the eye grounds. The choked disks, the tortuous thin arteries invisible in places, the distended veins, the fresh hemorrhages with areas of white patches present a typical picture as seen in Group 3.

complication of simple arteriosclerosis in group 2. The reasons are not clear why a few patients with simple arteriosclerosis develop into the rapidly progressing type with necrotic lesions in arterioles. The explanation advanced by Volhard and Fahr[2] assumed that a toxic inflammatory factor was added to a kidney already damaged by arteriosclerosis. They first clearly differentiated between essential hypertension with and without renal failure and described the histological lesions found in the kidneys of each type. To the case of hypertension with simple renal arteriosclerosis with no renal insufficiency they applied the term "benign"; and the term "combination form" or "malignant" was used to designate cases of hypertension which developed renal failure and uremia. They believed that the benign and malignant renal sclerosis were different forms of disease and not different stages. The considerable criticism that followed their publication dealt chiefly with their interpretation of the glomerular lesions of the malignant form. As stated by Fahr[22] the clinical differentiation between benign and malignant forms was readily accepted, but a unanimity of opinion concerning the pathogenesis of the two forms was difficult to obtain. Volhard[23] stated that after the criticism of Löhlein[24] he concluded that an added inflammatory factor was unnecessary to explain the tissue changes in malignant form. He also concluded that the lesions are the result of vasoconstriction of the afferent glomerular arterioles with subsequent nutritional disturbances in vascular system.

Fahr[25] maintained his opinion that the proliferative processes could not be produced by arteriosclerosis alone and that a toxic factor must be added. Among those who supported Fahr's theory were Von Mueller[26] and Meyer[27] and others. That the separation of the benign from malignant forms is justifiable from the clinical but not from the anatomical standpoint was held by Löhlein[28]. He stated that one deals not with two forms but only different stages of one process. Aschoff[29] did not recognize a (combination) malignant form. However, he believed that a "complication" form may exist; that is, a glomerulo-nephritis may become engrafted on a pre-existing renal arteriosclerosis. Arteriolosclerosis of the kidney was a term adopted by Herxheimer[30] for the condition resembling malignant renal sclerosis of Fahr. He disagreed with the histological distinction between benign and malignant forms of renal arteriosclerosis, and maintained that they are terms applied to different stages of the same process and not to separate forms. Jores[31] believed, too, that malignant and benign forms were different only in degree of arteriosclerotic involvement of smaller arteries. In the benign form he believed there was a focal arteriosclerosis of arterioles while in the malignant form there was a diffuse involvement of arterioles with disintegration of glomerular units.

In an intensive review of 420 cases of primary hypertension Bell and Clawson[18] found 36 cases with renal insufficiency; 27 of the 36 cases had a slowly progressive form of renal failure ending in uremia. The remaining nine cases were characterized by uremia coming on rapidly. Histologi-

cally there was necrosis of afferent glomerular arterioles with infarcted glomeruli. In four of the nine cases, acute inflammatory changes were seen in a few glomeruli. For the nine cases they applied the term "chronic hypertension with acute uremia". The syndrome of malignant hypertension was clearly defined by Keith, Wagener, and Kernohan[5]. They described the typical retinal changes and rapid downward course in conjunction with functional failure, not of one organ, but of several organs simultaneously. In their work they emphasized the importance of finding hypertrophy of the media of the arterioles of the skeletal muscles and of internal organs. They maintained that this hypertrophy indicates severe hypertension with diffuse vascular involvement and that the ultimate prognosis is bad.

Fishberg[32] did not see any essential difference between the benign and malignant forms. He used the term "malignant phase of essential hypertension" to describe those cases usually called malignant hypertension. The so-called malignant form, he stated, comes on gradually in the course of benign hypertension.

More recently Klemperer and Otani[33] discussed this subject at length. In conclusion they stated that essential

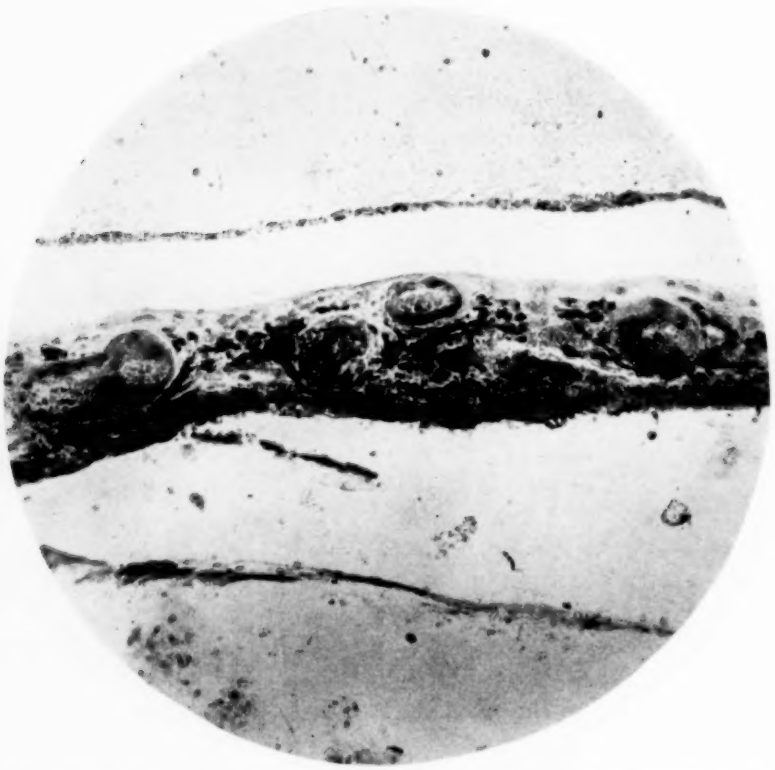


FIG. 7. (Group 3). Section from eye seen in figure 6. The arterioles of the retina show necrosis of the walls with almost complete obliteration of the lumina. Hematoxylin and eosin stain.

hypertension with renal failure may be associated either with a slowly progressing type of arteriosclerosis leading to renal failure or with a more rapidly developing vascular change in which severe renal atrophy is absent. This latter form is the "malignant" phase, and must be divided into two classes based on vascular lesions. In one there was necrosis of the arterioles with extreme cellular intimal thickening of larger interlobular and arcuate arteries and degenerative, proliferative, and slight exudative focal glomerular lesions. They believed that an ischemic mechanism is responsible for these changes, and they designated these cases as the accelerated atherosclerotic form. In the other form they observed necrotic lesions associated with perivascular inflammatory reaction, endarteritis and periarteritis. They recognized this latter form in two cases; in both cases a definite morbid process was present, recognized as toxic in origin. For such cases they used the term arteritic form of malignant nephrosclerosis. After carefully restudying our material several times we failed to discover more than one case which would fulfil the requirement of the arteritic type. In this case there was a periarteriolar leucocytic infiltration with a proliferative endarteritis. We were unable to recognize an additional toxic factor either clinically or at autopsy. From the results of our observations we favor the view adopted by those who believe that no additional inflammatory influence is necessary for the development of the change seen in the so-called malignant stage. There are undoubted cases coming within the malignant class that represent the effects of a toxic arteriosclerotic combination. Such cases are described by Klemperer and Otani[33] and appear to be identical with Fahr's descriptions.

Attention must be directed to the fact that in group 3 (malignant), there are various degrees of arteriolar damage. Vascular lesions may range from the pre-necrotic stage characterized by advanced arteriolosclerosis with complete occlusion of the lumina of arterioles to an extensive arteriolonecrosis accompanied by peri-arteriolar and interstitial leucocytic reactions. Necrotic lesions of the arterioles may be sparsely scattered throughout the kidney being observed only after thorough search or by serial sections; or they may be so numerous that in every section many are seen. As shown in table 1 all patients that fulfill the requirements for a place in group 3 do not die of renal insufficiency. Those patients with the most fulminating form of renal failure dying of sudden onset of uremia had the most destructive forms of necrotic lesions in the kidney. Hypertrophy of the media of arterioles in skeletal muscles, and in internal organs has been emphasized by Kernohan, Anderson, and Keith[34] in cases of severe benign and malignant hypertension. They believed this hypertrophy of the media indicated a poor prognosis. Hypertrophy of the media in arterioles of skeletal muscles was present in some cases in group 2 as well as in all cases of group 3. With respect to hypertrophic changes in the media of renal arterioles there was more uncertainty. In some kidneys from both groups 1 and 2, moderate medial thickening was frequently seen. This thickening was found

not always to be hypertrophy of muscle tissue but due in places to degenerative changes in the media. We believe that medial hypertrophy may exist in arterioles of internal organs but it is not a constant feature of any group. On the other hand hypertrophy of the media in arterioles of skeletal muscle is a constant feature of group 3 and is associated with persistent and severe hypertension.

Summary

1. Three hundred and seventy-five cases of essential hypertension are analyzed. On each of these postmortem examination was made.

2. The cases are divided for convenience of study into three stages: functional, arteriosclerotic, and arteriolonecrotic. The clinical signs and symptoms and the causes of death in each stage are considered.

3. Retinal changes were observed typical of the various stages.

4. Detailed postmortem pathological data, gross and microscopic, are presented covering weight of hearts, size and structure of kidneys, arteriosclerosis, and necrosis of blood vessels of involved organs.

5. Unifying features of all stages are hypertension, cardiac hypertrophy, and arteriosclerosis. The chief complications are apoplexy, heart failure, and renal failure. Arteriosclerosis of the renal vessels is a constant and characteristic feature of essential hypertension at autopsy. Particular attention is given to the syndrome of so-called malignant hypertension.

6. Histologically the principal lesion is an arteriosclerosis. The wide variety of symptoms and signs appears to depend upon the extensiveness, the rate of progress, the severity, and the location of the arteriosclerosis.

7. The clinical and histological observations on group 3 (so-called malignant hypertension) differ from those in group 2 (benign) only in degree. All of the symptoms and histological lesions observed, we believe, may be produced by arteriosclerosis alone.

REFERENCES

[1]Volhard, F.: in Handbuch d. inneren Medizin, G. von Bergheim und R. Staehlin, 1931, Julius Springer, Berlin, vi, part 2, 1556.

[2]Volhard, F., and Fahr, T.: Die Brightische Nierenkrankheit, Pathologie und Atlas, 1914, Julius Springer, Berlin.

[3]Murphy, F. D., and Grill, J.: So-called malignant hypertension; a clinical and morphological study, Arch. Int. Med., 1930, xlvi, 75-104.

[4]O'Hare, J. P., and Walker, W. G.: Arteriosclerosis, Arch. Int. Med., 1924, xxxiii, 343-349.

[5]Keith, N. M., Wagener, H. P., and Kernohan, J. W.: The syndrome of malignant hypertension, Arch. Int. Med., 1928, xli, 141-188.

[6]Fishberg, A. M., and Oppenheimer, B. S.: The differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases, Arch. Int. Med., 1930, xlvi, 901-920.

[7]Wagener, H. P.: Retinal vascular changes in hypertension, Ann. Int. Med., 1930, iv, 222-226.

[8]McGregor, L.: Histological changes in the renal glomerulus in essential (primary) hypertension; study of fifty-one cases, Am. Jr. Path., 1930, vi, 347-366.

[9]Allbutt, C.: Disease of the arteries including angina pectoris, 1915, Macmillan and Company, London, i, 381.

[10]Mahomed, F. A.: Chronic Bright's disease without albuminuria, Guy's Hosp.

Rep., 1881, xxv, (Third Series), 295-416.

[11]Moschcowitz, E.: Hypertension; its significance, relation to arteriosclerosis and nephritis and etiology, Am. Jr. Med., Sci., 1919, clviii, 668-684.

[12]Ayman, D., and Pratt, J. H.: Nature of the symptoms associated with essential hypertension, Arch. Int. Med., 1931, xlvii, 675-687.

[13]Davis, D.: The nature of the symptoms in essential hypertension, Am. Jr. Med. Sci., 1931, clxxxi, 850-857.

[14]Riseman, J. E. F., and Weiss, S.: The symptomatology of arterial hypertension, Am. Jr. Med. Sci., 1930, clxxx, 47-59.

[15]Rolleston, H.: High blood pressure from the clinical aspect, Lancet, 1926, ii, 1203-1207.

[16]Fishberg, A. M.: Hypertension and nephritis, 1930, Lea and Febiger, Phil., 410.

[17]Herxheimer, G., and Schulz, K.: Statistisches zum Kapitel Bluthochdruck, Herzhypertrophie, Nierenarteriolosklerose, Gehirnblutung nach anatomischen Befunden, Klin. Wchnschr., 1931, x, 433-438.

[18]Bell, E. T., and Clawson, G. J.: Primary (essential) hypertension; a study of four hundred and twenty cases, Arch. Path., 1928, v. 939-1002.

[19]Shapiro, P. F.: Malignant nephrosclerosis; pathogenesis, Arch. Int. Med., 1931, xlviii, 199-233.

[20]Russell, D. S.: A classification of Bright's disease, Med. Res. Council, 1929-30, Spec. Rep. Ser., No. 142, His Majesty's Stationer's Office, 131.

[21]Van Slyke, D. D., and Others: Observations on courses of different types of Bright's disease and on resultant changes in renal anatomy, Med., 1930, ix, 257-386.

[22]Fahr, T.: Über die Beziehungen von Arteriolosklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat., 1922, ccxxxix, 41-63.

[23]Volhard, F.: in Handbuch d. inneren Medizin, G. V. Bergheim und R. Staehlin, 1931, Julius Springer, vi, part 2, 1561.

[24]Löhlein, M.: Über Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path., 1917, lxiii, 570-632.

[25]Fahr, T.: Quoted by Volhard. (footnote 22).

[26]von Mueller, F.: Veröffentlichungen aus dem Gebiete des militäre Sanitätswesen 1917, A. Hirschwald, Berlin, lxv, 45.

[27]Meyer, O.: Über das Vorkommen und die Bedeutung entzündlicher Gefässveränderungen in den Nieren mit besonderer Berucksichtigung der Glomerulitis, der sekundären und genuinen Schrumpfnieren, Verhandl. d. deutsch. path. Gesellsch., 1921-23, xix, 352-363.

[28]Löhlein, M.: Zur Nephrocirrhosis Arteriosclerotica, Med. Klin., 1918, xiv, 136-137.

[29]Aschoff, L.: Quoted by Volhard in Handbuch d. inneren Medizin, G. V. Bergheim, und R. Staehlin, 1931, Julius Springer, Berlin, vi, part 2, 1559.

[30]Herxheimer, G.: Über Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat., 1924, ccli, 709-717.

[31]Jores, L.: Über den pathologischen Umbau von Organen (Metallaxie) und seine Bedeutung für die Auffassung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrozirrhosen) und der Arteriosklerose; nebst, Bemerkungen über die Namengebung in der Pathologie, Virchows Arch. f. path. Anat., 1915, ccxxi, 14-38.

[32]Fishberg, A. M.: Hypertension and nephritis, 1930, Lea and Febiger, Phil., 418.

[33]Klemperer, P., and Otani, S.: "Malignant nephrosclerosis" (Fahr), Arch. Path., 1931, xi, 60-117.

[34]Kernohan, J. W.; Anderson, E. W., and Keith, M.: The arterioles in cases of hypertension, Arch. Int. Med., 1929, xliv, 395-423.

Hypertension*†

A Study of Two Hundred Two Cases Followed for an Average of Ten Years—With Remarks on Causes and Treatment.

By J. M. Blackford, M.D., F.A.C.P., and J. N. Wilkinson, M.D.,
Seattle, Washington

HYPERTENSION has been the subject of hundreds of articles and a considerable number of books during the last twenty years. Cardiovascular consultants and insurance companies have furnished most that is written on end results.

Actuarial experience gives an extremely gloomy picture of the outlook for hypertension. Insurance records are based, however, on approximately 90 per cent males and exclude, for manifest reasons, all hypertension cases discovered at the time of examination. Cardiovascular consultants see chiefly cases who are sick with circulatory disturbances and hence see a more or less selected group of patients. We have been able to find no follow-up studies on unselected hypertension cases.

Two years ago we reported a series of cases obtained by reviewing 10,000 consecutive histories of general examinations made before 1925. We took for study all cases whose blood pressure was found definitely high, using cases in which the systolic pressure was reported as 175 plus or the diastolic pressure 100 plus. Cases with readings below these figures were omitted because there is some question to to whether temporary causes, particularly nervous, may occasionally give a reading up to these points. Thus we obtained a consecutive series of hypertension cases, unselected except by the fact that some complaint made them come in for a general examination.

Our clinic sees in each decade approximately an equal number of men and women, yet hypertension was found twice as frequently in women (64 per cent) as in men (36 per cent). In each decade between 30 and 70 years the percentage incidence of hypertension in women was approximately double that seen in men. Yet more than half of the women were without hypertensive symptoms, whereas hypertension in men was usually accompanied by symptoms. The large symptomless group of females with hypertension is not seen in cardiovascular clinics or by life insurance companies, and hence is not included in hypertensive follow-up studies.

*From the Mason Clinic, Seattle, Washington.

†Presented at the San Francisco Meeting of the American College of Physicians, April 6, 1932.

Follow-Up Study

A follow-up study made two years ago gave information on the condition of 202 patients after an average of eight years. One-half (50 per cent) were dead. The female mortality was 42 per cent, whereas the male mortality was 79 per cent. About three-quarters of all deaths resulted from hypertensive disease, usually failure of heart or of cerebral circulation and occasionally nephritis. One-quarter of all deaths resulted from other causes.

We have followed 101 patients living two years ago down to the present. The gross mortality now is 60 per cent, but female mortality is 50 per cent and male mortality is 82 per cent, after an average of ten years. No male with marked hypertension still survives. Of 66 females surviving, 39 (59 per cent) are relatively symptom free, whereas of 13 surviving males 3 (24 per cent) are relatively symptom free. Seven females are still alive in spite of marked or extreme hypertension discovered ten years ago.

Only two instances of recovery of a normal blood pressure have been noted.

These laborious follow-up studies and study of clinical histories have led to much reflection on the causes and treatment of hypertension.

Causes of Hypertension

Experimental hypertension has been produced by (1) various pressor substances, (2) removal of depressor nerves, (3) diffusely increasing intracranial pressure, and (4) experimental renal lesions which partially obstruct renal circulation. It should be noted that these experimental methods work through the sympathetic nervous system.

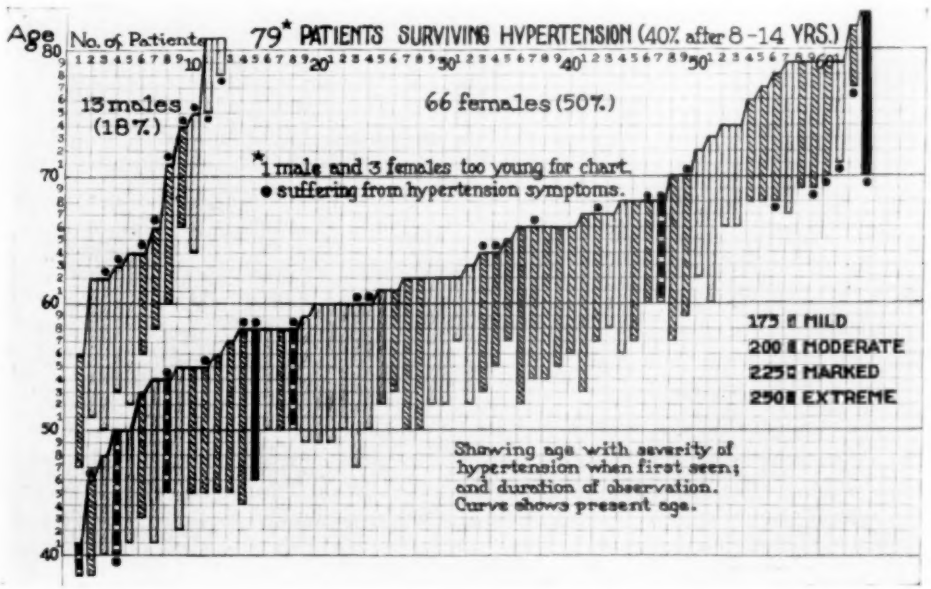


Fig. 1

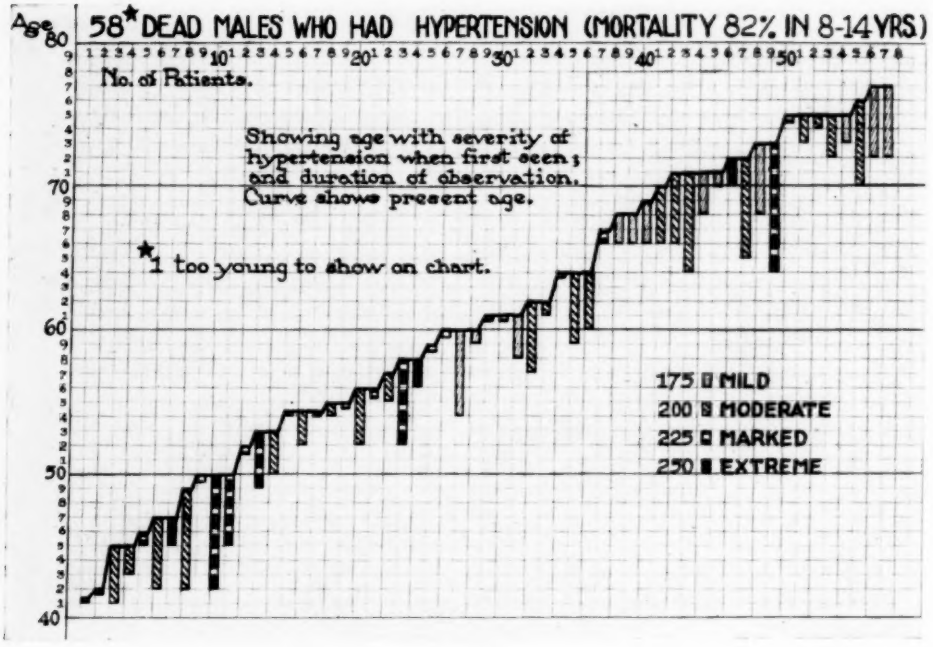


FIG. 2

Clinical hypertension has been variously classified. The classification that seems to us reasonably complete is:

1. Physiologic
2. Circulatory defects
3. Paroxysmal hypertension
4. Toxic
5. Renal
6. Neurogenous vasospasm

The last three groups include nearly all cases of clinical hypertension, and it is with these that we are here concerned.

Toxic hypertension includes cases due to known toxins which affect the kidneys, such as lead, mercury, and the toxins of the eclamptic state. Anaphylactic hypertension must be included here as well as the hypertension due to the toxic goiter. Hypertension due solely to toxic goiter is never high, rarely as high as 175 mm., and is relieved by thyroidectomy. Higher readings than these in toxic goiter cases are not relieved by thyroidectomy, being due to essential hypertension associated with, but not due to, thyrotoxicosis.

Renal hypertension is found with chronic interstitial nephritis, chronic urinary obstruction, and often with polycystic kidney disease. It would seem that, as with experimental renal hypertension, chronic lesions offering obstruction to renal circulation are accompanied by hypertension of a compensatory nature. When such chronic obstruction can be relieved (as with prostatic cases) a normal blood pressure will be restored if there is not too much renal damage. Apparently there is a defensive compensatory angio-

spasm which automatically raises blood pressure as necessary to give an adequate renal circulation.

Increasing intracranial pressure likewise automatically raises blood pressure sufficiently to maintain a cerebral circulation. Cushing's experiments have shown that when intracranial pressure is raised the blood pressure shows a corresponding rise.

We see, then, that the cerebral and the renal circulations, necessary to life, are preserved by a rise in blood pressure to compensate for chronic partial circulatory obstruction in these organs, and the rise persists during the period of obstruction. Chronic partial obstruction of the cerebral circulation by increased intracranial pressure results in early deaths unless relieved. In the renal circulation such chronic obstruction may exist for months or years, with increasing blood pressure to compensate for increasing renal damage.

Essential hypertension brings us to a group of cases in which the blood pressure is high, without evident pathology to account for it. By far the greatest number of cases of hypertension fall into this group. It would seem that some constitutional tendency in the vegetative nervous system is responsible for the condition rather than unrecognized gross or microscopic lesions or retention of toxins. We recognize a hypotensive group of people, who may live long lives because lack of nervous endurance makes it impossible for them to wear out physically. We should recognize a hypertensive group, in whom the constitutional tendencies of the vegetative nervous system lead to generalized angiospasm with resulting hypertension. Early in this state of affairs there are no clinical symp-

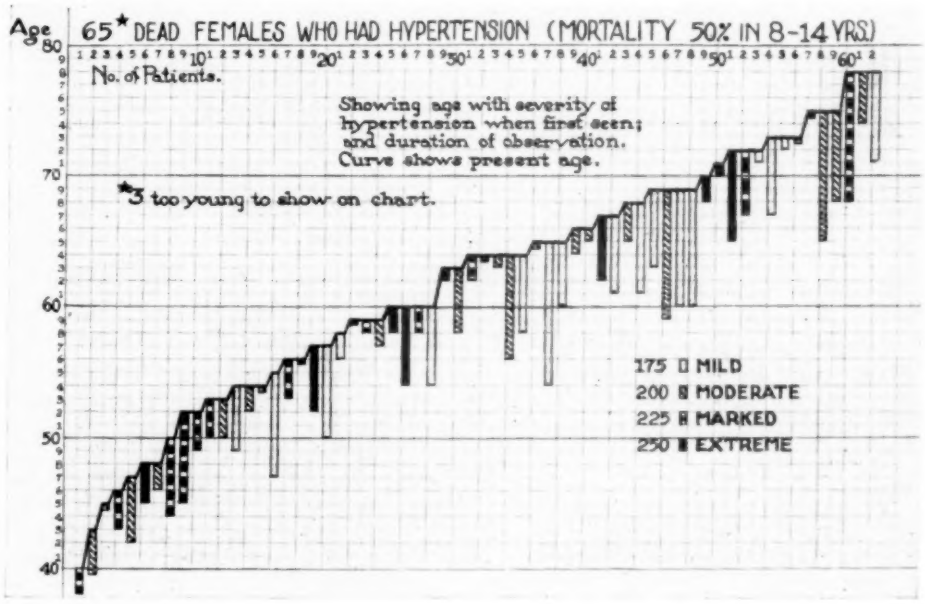


FIG. 3

toms and the patient may appear quite normal. Later, depending on the resistance of the vital organs and the arteries to stress, we see progressive wear on heart and vessels. Results of such hypertonicity of the neurovascular control of spasm vary from the early and acute breakdown, with arteriolar necrosis, of malignant hypertension in youth to the chronic myocardial and vascular degeneration of increasing age. In certain instances the patient may even reach a ripe old age relatively free from symptoms in spite of an extreme hypertension.

It has been stated that hypertensive disease runs in families. We have found a family history suggestive of hypertensive disease in more than one-third of all cases of hypertension, but approximately the same percentage of hypertension in family histories is found in all family histories of patients, regardless of complaints. In spite of these facts, most physicians feel that there is a strong family tendency toward hypertension in certain instances.

Available clinical and laboratory evidence suggests that hypertension must be regarded as the result of a generalized angiospastic state, a constitutional vascular hypertonus inherent in the individual. It rarely becomes evident before 40 years of age. It is far more serious in younger people. It is less serious but more frequently found in women than in men.

Treatment

Treatment based upon this conception becomes a matter of relief of stress, particularly mental stress, and of moderation of habits. Medical treatment is reserved for relief of complications, and these may not develop for many years. Cardiac failure is the usual symptom that requires relief, with cerebral vascular symptoms next most common. Sedatives, both mental and physical, are required; with all the reassurances and encouragement that can be given. Bromides, barbital derivatives, etc. are of great help.

Venesection is frequently indicated for relief of symptoms, particularly headache. The blood pressure is reduced only transiently by this procedure, yet subjective relief may last over weeks or months. Nitrites are occasionally valuable in relieving hypertensive headaches.

Weight reduction is always advisable in the obese. We usually prescribe a well balanced diet, low in salt and in proteid foods. Every effort should be made to avoid any dietary insufficiency leading to unnecessary anemia and loss of strength; and this can easily happen if the conscientious patient is advised to eat no meat or eggs.

Attempts at specific medication are always interesting. Aylen of Boston has found no drug of greater value than could be accounted for on a psychotherapeutic basis. To enumerate drugs recommended would make a long list. We may mention watermelon seed, mistletoe, liver extract, potassium sulphocyanate, and bismuth subnitrate as recent suggestions that have not stood the test of therapeutic practice. Possibly some day some specific remedy may be discovered. It seems to us doubtful if we can change constitutional tendencies inherent in the patient, even though we may greatly

relieve symptoms which result from the continuation of these tendencies.

Fear, anxiety, and introspection are the most troublesome symptoms associated with hypertension. Unfortunately they are sometimes implanted and fostered by the physician. Fear of the consequences of hypertension causes more suffering for many patients than do all the later severe complications which may occur.

Summary

In conclusion, we find that:

1. Hypertension is twice as frequently found in women.

2. The mortality rate after ten years is twice greater in men.

3. Hypertension results from a constitutional hypertonicity of the autonomic neurovascular control in the large majority of instances and is a compensatory angiospasm in the others.

4. Treatment of uncomplicated hypertension is a matter of mental and physical hygiene rather than of drugs.

5. Treatment of late results of hypertension requires skillful use of medical and physical measures, added to psychotherapeutic measures.

6. The physician who is a good and cheerful psychologist will be the most successful in relieving the symptoms of hypertensive cardiovascular disease.

Thallium Poisoning

A Report of Three Cases*

By James Lehman, M.D., and Leo Gaffney, M.D., *Cleveland, Ohio*

THE increasing incidence of thallium poisoning, following the use of depilatory creams has prompted us to report the following cases which have been under observation recently at the Cleveland Clinic. In all three cases the history included a similar statement, namely, that the patient had used "Koremlu", a depilatory cream.

Several cases of thallium poisoning have been reported. Lansbury[1] of the Mayo Clinic reported the first case. A short time later, Duncan and Crosby[2] of the Cleveland Clinic reported a similar case. Greenbaum and Shamberg[3] have also reported cases. The Bureau of Investigation of the American Medical Association has published a report[1] on the chemical analysis of "Koremlu", and branded it a dangerous depilatory, containing seven per cent of thallium acetate. Sabouraud, after an extensive experience with the use of thallium as a depilatory is said to have given up its use. (See Paris Letter, Jr. Am. Med. Assoc., Jan. 18, 1930.) Moreover, Sabouraud's original preparation called for an ointment with not more than one per cent of thallium acetate and the use of the ointment in quantities not larger than the size of two kernels of wheat, to be applied not more than twice a day. In the directions for the use of "Koremlu", no mention is made of the amount to be used, nor the frequency of its application.

Case I

A woman, 39 years of age, came to the Clinic on March 26, 1931, complaining of pain in both legs. She had been well until two weeks previous to her visit to the Clinic, when she noticed numbness and tingling in her toes. This progressed gradually until the entire lower extremities were involved. Two days before her admission to the Clinic the numbness was replaced by pain which was most severe in the knees and ankles, and it was necessary for the patient to remain in bed. The pain was confined to the lower extremities and was relieved somewhat by the application of heat.

The family and personal history had no bearing upon the existing condition.

The significant findings in the physical examination were the following: the hair was well nourished and was distributed normally, except for hypertrichosis of the face. The tonsils, which were of moderate size, were imbedded and contained débris and liquid pus. A complete x-ray examination of the teeth showed one carious tooth, periapical infection about the first and second premolars of the upper left, first and second premolars of the upper right, first molar of the lower left and second molar of the lower right jaw. The patient was advised to have these teeth extracted. The tongue was heavily coated, and a slight

*From the Cleveland Clinic, Cleveland, Ohio. Submitted for publication, November 12, 1931.

tremor was present. A special neurological examination by Dr. W. James Gardner gave the following positive findings: pain, deep tenderness and muscular weakness of both lower extremities, moderate hyperesthesia of the skin with no definite level, diminished plantar, patellar, Achilles and triceps reflexes.

The patient was admitted to the Cleveland Clinic Hospital with a diagnosis of toxic neuritis, carious teeth, and chronic tonsillitis. Further questioning of the patient brought out the fact that she had been using a depilatory cream, "Koremlu", applying it twice a day. We felt justified, therefore, in making a diagnosis of peripheral neuritis, due to the toxic effects of thallium absorbed from the depilatory cream.

TREATMENT

During her stay in the hospital, the patient was put at absolute bed rest and external heat was applied to the lower extremities. Passive motion and massage were instituted. She was also given an alkaline diuretic. The six diseased teeth and the tonsils were removed. On April 8, 1931, the patient was discharged somewhat improved.

On April 29 she reported that all pains had disappeared with the exception of some discomfort in the legs when fatigued. There was still a sensation of numbness in all the toes. Fatigue was marked, but there was good power in the dorsi-flexors.

The latest report from the patient was on July 22 when she stated that she was free from pain except for a slight prickling

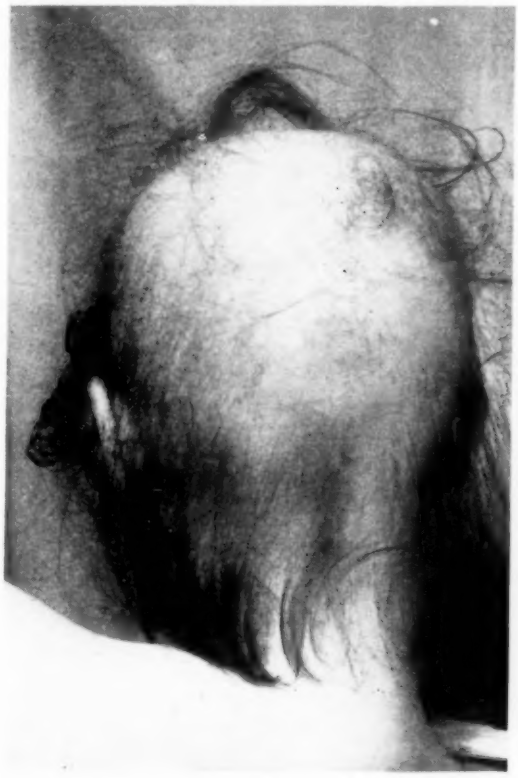


FIG. 1. Marked alopecia after using "Koremlu Cream" for removal of hair from the face.

sensation or partial numbness after walking rapidly or great distances. For a month past she had noticed that her hair had been falling out.

CASE II

A woman, 28 years of age, was admitted to the Cleveland Clinic Hospital on April 21, 1931, complaining of aching pain in the thighs and legs, impairment of sensation in legs, arms, feet and hands, abdominal cramps not associated with nausea or vomiting, generalized weakness, inability to walk, loss of cranial, axillary and pubic hair, speech impairment, menstrual irregularity, restlessness, irritability and insomnia.

The patient was well until three and one-half months previous to her admission to the hospital. The symptoms were noticed from two to three weeks after she had started using "Koremlu" cream for the removal of hair from the face. This cream was purchased from a department store in Akron, Ohio, at a cost of $10.00 for a small jar. The patient had been applying the cream once a day until she came to the hospital.

The first symptom noticed was the aching pain in the legs, especially in the calf muscles. After about a month she noticed that she was losing the power of her legs which became complete three weeks previous to her admission to the Clinic. Following this, abdominal cramps developed, which gradually increased in severity. There was no nausea, vomiting or diarrhea on taking of food. About six weeks after she started using the cream, her cranial, pubic and axillary hair began to fall out until almost complete alopecia resulted. The hair on the face was not affected. Generalized weakness gradually developed including impairment of sensation in the legs, arms, hands, and feet; the menstrual flow became very scant; the patient became restless and could not sleep. She had lost about five pounds.

The significant findings in the physical examination were as follows: The skin was rather dry and smooth; there was very little hair on the arms or legs and the loss of cranial hair was marked; the scalp was dry and scaly; the hair was dry and easily pulled out. The eyebrows showed loss and what remained were easily pulled out. The tongue was coated and rather dry. The tonsils which were of moderate size contained débris and some infectious material. The abdomen was slightly tender just below and to the left of the umbilicus but no masses were found and there was no rigidity.

Marked tenderness was present over the posterior aspect of the thighs, and over the anterior and lateral portions of the legs; there was suggestive impairment of sensation over the inner aspect of the right leg; the muscles, especially of the thighs and legs, were flabby. The patellar and biceps reflexes were fairly active and equal; there was some numbness and tingling in the legs, feet and hands. Loss of motor power in the legs and arms was noted and the patient could stand for a few minutes only.

Dental examination revealed no devitalized teeth and no evidence of periapical infection; there were two extensive restorations, and the patient was advised to have these teeth tested for vitality, and to have them extracted if necessary.

Neurological examination revealed impaired gait, toe drop, bilateral partial paralysis of the lower extremities; bilateral atrophy and hypotonicity of the lower extremities; paresthesias of the legs and hands and impairment of sensation of the legs. The patient's voice was husky and she was mentally depressed.

About a week before her admission to the hospital the patient refused to have an exploratory laparotomy in order to determine the cause of the abdominal cramps.

Treatment

The patient was given 3500 c.c. of fluid over a twenty-four hour period. Sedatives were administered as indicated for pain or insomnia. A cradle was placed over the lower extremities to protect them from the weight of the bed clothes, and the soles of the feet were supported to overcome the footdrop. Calcium chloride was administered intravenously in doses of 20 c.c. of a five per cent solution every second day. After five injections, the symptoms became worse and this treatment was discontinued.

Heat, light and massage were applied to the lower extremities.

When the patient was discharged after twenty days, her condition was slightly improved. The hair was still falling out but the pain in the extremities was less severe and the abdominal cramps were not so constant. The patient was less restless and slept better. She was still unable to walk, however, and the leg muscles showed increasing wasting. Bilateral toe drop and positive Babinski were still present and the reflexes were still diminished. Numbness and tingling were still present in the hands and feet. The general condition of the patient was somewhat improved, however, and she was less depressed.

A report from the patient's physician on July 7 stated that she had shown slight improvement since her return home but was still confined to her bed and unable to walk. Pain was still present in the legs but the abdominal cramps had disappeared. The leg muscles showed a moderate degree of wasting. The cranial hair had begun to grow and was about one and one-half inches long. The patient was receiving massage and passive motion of the legs daily. She still required sedatives occasionally.

Case III

A woman, 27 years of age, came to the Clinic on July 8, 1931, complaining of pains in the legs. The pain began about August 30, 1930, three weeks after she began using "Koremlu Cream" for the removal of hair from the face. In spite of the fact that the pain became worse as the patient continued to use the depilatory, she did not and had not to date connected the use of the cream with the pains, which she described as being dull and aching and made worse by motion. After two months the pain became so severe and constant that she was confined to bed. Her family doctor could not find the cause of the trouble and his treatment gave no relief. He finally sent her to a hospital in Pittsburgh, where a thorough study was made of the case. Just before going to the hospital, she began having cramplike pain in the abdomen. A gastro-intestinal series was done but no pathological condition was demonstrated. While in the hospital she stopped using the

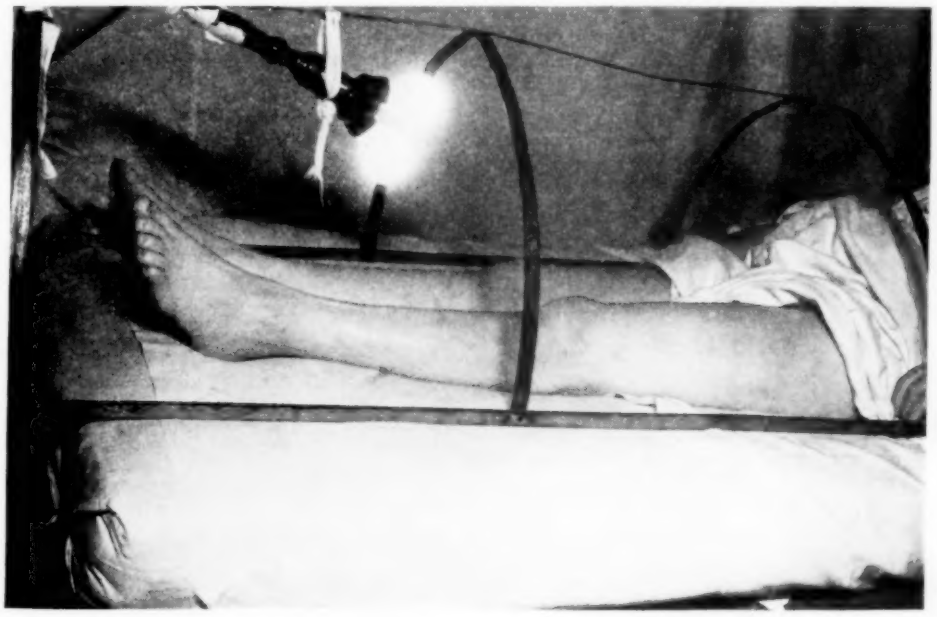


Fig. 2. Foot drop and muscular atrophy of lower extremities in thallium poisoning.

cream and at the end of three weeks she felt somewhat improved and was discharged. After she returned home she began using the cream again and the pain in the legs and abdomen returned. Associated with the pains at this time was a marked sensitiveness of the feet, which prevented walking.

After trying various treatments for two months she decided to go to Hot Springs, Arkansas, to take the baths. A few days after arriving there she finished her second jar of "Koremlu Cream" and was unable to buy any at Hot Springs. She took a series of baths and her health began to improve. She remained at the Springs for about four weeks. At the end of that time, nearly all the pain was gone and she was able to walk without any discomfort. The patient returned home and enjoyed freedom from pain for two months, during which time she was not using the cream. A short time later she bought another jar and began using it each night, and continued to use it up to the time of her admission to the Clinic. About three weeks later, the pain in the legs, and sensitiveness in the feet and the cramps in the abdomen returned. The patient mentioned to several doctors that she was using "Koremlu Cream" but they all assured her that this could not be the cause of her trouble. She had had no loss of cranial, axillary or pubic hair.

Examination at the Clinic showed a well nourished woman, not actually ill. The only positive physical findings were atrophy of the left calf and thigh, to the extent of about one and one-half inches, and tenderness along the course of the nerves of the legs. No attempt was made to isolate thallium from the urine.

In view of the fact that the pain first occurred shortly after the patient started using the "Koremlu Cream" and because the pain disappeared when on two occasions she discontinued the use of the depilatory, we felt that we were justified in making a diagnosis of chronic thallium poisoning. The patient was advised to discontinue the use of the cream and to have light massage and light treatment for the legs.

REFERENCES

[1]Lansbury, J.:A case of thallium poisoning. Pro. of the Staff Meet. of the Mayo Clinic, 1930, v, 323-325.

[2]Duncan, W. S., and Crosby, E. S.: A case of thallium poisoning following the prolonged use of a depilatory cream, Jr. Am. Med. Assoc., 1931, xcvi, 1866-1868.

[3]Greenbaum, S. S. and Shamberg, E.: Reports of thallium acetate poisoning following the use of Koremlu. Jr. Am. Med. Assoc., 1931, xcvi, 1868.

[4]A dangerous depilatory containing thallium acetate, Jr. Am. Med. Assoc., 1931, xcvi, 629-630.

Newer Aspects in Paradentosis (Pyorrhea)*

By Hermann Becks, M.D., D.D.S., *San Francisco, California*

OUR conceptions of the true anatomic conditions in the region of the tooth supporting tissues or "paradentium" (Weski) have recently undergone a definite change through the work of contemporary histologists and clinicians (Boenheim, Citron, Gottlieb, Häupl, Lang, Loos, Weinmann, Weski).

This change in our ideas brought about a renewed interest in the etiologic and pathogenetic questions in paradentosis in all countries. Today after twelve years have elapsed there are still questions of fundamental importance which are under debate, the solution of which may not be reached in any short space of time. These are mainly histologic details which, however, are of immense importance to the practicing dentist; these he must know in order to be able to understand the etiology, pathogenesis, and therapy of the disease. Before these new conceptions can be adopted it will be necessary to throw overboard many antiquated theories, otherwise we will become involved in a maze of complicated ideas, from which it will be very difficult to extricate ourselves.

One of the greatest advances in the last few years in this particular field has been in the new terminology which was decided upon by vote of the Eighth International Dental Congress, at Paris, in August, 1931. I refer to the term "paradentosis", which replaces the old term "pyorrhea".

A classification has been adopted which includes all known types of the disease formerly called "alveolar pyorrhea", "periodontoclasia", etc. It groups all cases according to their clinical symptoms. The designations, as such, have been chosen to point to the pathogenesis of the disease.

Classification

1. Marginal suppurative gingivitis
   Local manifestations:
   Superficial inflammation with discharge of pus at the gingival margin.
   Calculus
   No distinct pocket formation
2. Paradentosis
   a. Profound simple paradentitis
      Local manifestations:
      Deep pocket
      Pus
      No loosening of the teeth
   b. Diffuse dystrophy
      Local manifestations:
      Irregular atrophy
      Migration or loosening of teeth
      No pus

*Presented at the San Francisco Meeting of the American College of Physicians, April 5, 1932.

c. Complicated dystrophic paradentitis
Local manifestations:
Deep pocket
Pus
Eventual loosening of teeth or migration or both
The final phase of a, b, and c, is:
Loosening of teeth, deep pockets, pus.

3. Alveolar atrophy
a. Pre-senile atrophy (atrophia praecox)
Local manifestations:
Early recession of the gingival margin
Horizontal atrophy of bone
b. Senile atrophy
Local manifestations:
The same as under "a", but at an advanced age.

It is of especial importance to observe that in this classification the marginal suppurative gingivitis, which was formerly designated as "pyorrhea", has been separated from the large group of paradentosis. This has been done because such a marginal suppurative gingivitis with a slight discharge of pus exists over a period of years without developing into a paradentosis; i.e., without involving the deeper parts of the paradentium. Of course this condition may suddenly become an ulcerative type of gingivitis or paradentitis, which in the course of time involves the bone and leads to the clinical picture of paradentosis.

On the other hand the alveolar atrophy has also been separated from paradentosis because it represents a special group of diseases.

Paradentosis itself is subdivided into three main groups, which include all types of this disease of the paradentium known at the present time. However, it may be emphasized that this classification is only tentative and has been adopted in order that practitioners of medicine and dentistry, as well as research workers, may be provided with a uniform working basis. Doubtless, it would be easier for the practitioner if a classification could be made which includes the etiological factors; i.e., if we could speak of a diabetic paradentosis, of a scorbutic or an arthritic paradentosis. However, our research has not progressed that far as yet.

There is a very definite conception of the disease connected with this new designation, which means more than just "pyorrhea", which is defined as "pus discharge from the gum pocket". We must try more than ever to forget the symptom of pus in establishing the diagnosis, since this does not indicate the condition of the tissues. Our observations should be directed toward the morphological and clinical changes to be treated and here we must be interested first in the factors which have led to these changes in the paradentium.

The paradentosis problem is a part of a constitutional problem. The *individual disposition* forms the nucleus of the susceptibility to paradentosis, which on the one side occurs as a result of systemic disease and on the other on the same basis as the disease itself. We speak of endogenous factors in collusion with well known exogenous factors, by means of which the paradentosis has gained a foothold. At the present time we have very little scientific information about these en-

dogenous factors, which influence the occurrence of paradentosis.

In the etiology we differentiate today between two fundamental forms of paradentosis: First, that which is characterized by an inflammatory disappearance of marginal tissue; and second, one with a generalized tissue destruction. Although we have gained a vast amount of knowledge concerning the first type in etiologic and histopathogenic respects, there still exists a great hiatus in our knowledge of the etiology of the genuine type, which seems to be based on an abnormal condition in bone apposition and resorption; i.e., a lack of stability in bone metabolism (Loos, Weski). Several times Loos has expressed the opinion that this form of paradentosis, which is based on the instability of the bone metabolism, occurs as a result of an osteopathy with an endocrine genesis. We have not advanced beyond this point as yet and only recently in our laboratory at Hooper Foundation we were able to furnish for the first time the scientific proof of this theory by means of diet experiments in animals.

We will omit from the following discussion the marginal suppurative gingivitis, which is caused essentially by exogenous or local factors and concern ourselves only with that form of paradentosis which cannot be explained by local irritation only and must, therefore, fall in the field of investigation of the general system. We do not know definitely whether or not a special constitution of the capillary system of the paradentium or of the osseous system (Loos) brings about a susceptibility to the disease. However, we may accept this as an hypothesis. At the present time, in all countries, workers are feverishly active in the endeavor to establish a relation between paradentosis and diseases of metabolism, diseases of the blood forming organs, hormonal disturbances, and disturbances of the vegetative nervous system. Even though they have not become pathognomonic for paradentosis as yet, all investigations and examinations in this direction are extremely important for paradentosis as a medical problem.

If we start with the supposition, as already mentioned, that the osseous part of the paradentium primarily gives a constitutional basis for paradentosis or that through other endogenous factors the alveolar process undergoes changes which lead to the typical atrophic and dystrophic symptoms, an especially interesting field of investigation is that of calcium metabolism.

In the year 1929, I reported that the electrolytic content of the saliva in patients suffering from the so-called diffuse atrophy deviated from the normal. This was of importance because no studies in mineral metabolism had as yet been made. At that time I reported that in the saliva of seventeen cases of diffuse atrophy of the alveolar process the potassium and sodium contents were increased and the calcium and phosphorus contents were decreased as much as 25 per cent. At the same time a publication of Citron appeared covering the examination of serum calcium in patients with paradentosis and a few others along this same line followed (Kauschansky, Herz, Weinmann, Becks). Citron examined eighty-seven cases of para-

dentosis, which had not been classified exactly, for serum calcium and potassium. He also examined the basal metabolism, the specific dynamic action of foods, and microscopically the capillaries of the gum tissue. In these patients all laboratory findings showed some metabolic disturbance. Citron related these disturbances to a primary dysfunction of the glands of internal secretion. He classified them as thyroid, parathyroid, ovarian, and pituitary types of paradentosis and believed that they were a symptom of a general systemic disease. In these eighty-seven cases he found that the serum calcium value was between 8 and 9 mg. per cent in three cases, between 10 and 12 mg. per cent in seventy-three cases, and between 13 and 17 mg. per cent in eleven cases. This means that in the majority of cases suffering from paradentosis, the serum calcium content was increased.

Weinmann, one of the most enthusiastic supporters of the so-called diffuse atrophy as an independent disease, which is designated in the new classification as diffuse dystrophic type of paradentosis, found approximately the same percentages; while Herz found normal calcium values in most of his cases. Kauschanksy found calcium values above 11 mg. per cent in 35 per cent of his cases (he examined 135 patients with "alveolar pyorrhea").

The weakest point in these publications is that the cases of "alveolar pyorrhea" were not classified. Frequently in scientific publications we find the same confusion that is prevalent among practitioners; i.e., a lack of the exact details of diagnosis. Weinmann is the only one who made examinations exclusively of cases with diffuse dystrophic paradentosis, while a mixed material was used by other investigators, which may be composed to a large extent of cases of simple gingivitis, designated today as marginal suppurative gingivitis, and naturally in these cases we cannot expect to find any change in calcium metabolism. The conclusions which were drawn from these findings are, therefore, without value.

The cases of paradentosis which I have examined within the last year have been grouped according to the new classification. Only cases of the diffuse dystrophic type were examined; i.e., cases of Gottlieb's diffuse atrophy. These were cases which roentgenologically showed extreme resorption of the alveolar process. The patients were young adults between the ages of twenty and thirty-five years. The resorption was too far advanced to be accounted for by the age of the patient and the degree of inflammation present. There existed a tendency to migration and slight loosening with pocket formation.

The majority of cases—there were only a very few exceptions—showed *an increase of the amount of serum calcium;* i.e., we confirmed the statements of Citron, Weinmann, and Kauschansky. The serum calcium values reached as high as 18.15 mg. per cent. The cause of this increase in the amount of serum calcium is still problematic. Citron believes that the hypercalcemia must be traced to an increased function of the parathyroids. He bases his conception on the fact that an elimination of the parathyroid function leads to an increase of

potassium and to a decrease of the calcium in the blood while the reverse condition would mean an *over-function* of the gland. Experimentally this has been proven by the administration of large doses of Collip's parathormone.

The potassium-calcium quotient of normal cases gives a practical index which can be used in determining an unbalanced condition. If the normal potassium content is about 20 mg. per cent and the normal calcium value lies between 9 and 11 mg. per cent, the potassium-calcium quotient is about 1.6 to 2.0.

In the thirty-seven examinations of Weinmann, in which he found hypercalcemia twenty-seven times, the potassium-calcium quotient was below normal only eight times, while it was above seven times. This vacillation of the quotient, of course, does not allow any conclusions concerning the participation of the parathyroids in this process. Weinmann even expresses doubt that the increase in serum calcium may be traced back to a mobilization of calcium salts from the bone.

In our examinations, we found that the serum potassium value was just as frequently increased as decreased. *However, the striking fact was established that in the twenty-four cases examined, eleven cases showed a low, four a high, and nine a normal potassium-calcium quotient.* This seems to show that the increase in blood serum calcium parallels a relatively low potassium value, which led in the majority of cases to the low potassium-calcium quotient. On the other hand a relation to an endocrine disturbance seemed to exist in our cases, which is in contrast to the findings of Weinmann.

The porotic jaws which we observe so very frequently in roentgenograms suggest that a disturbance in the balance of bone apposition and resorption may be present. Whether this disturbance is produced by the endocrine system, by a deficient diet, or constitutional anomalies is rather a secondary question. First, it must be proven scientifically that such a disturbance really exists and for this purpose the calcium analyses of the blood serum alone are of no value whatsoever. As already shown, they can be used in connection with potassium analyses and may help explain the participation of the endocrine system. However, in order to be able to draw conclusions concerning the participation of the osseous system we must consider other factors. Of these I might mention the phosphorus metabolism in its relation to calcium metabolism; further, the carbon dioxide capacity of blood, the basal metabolism, and the specific dynamic action of proteins.

From the investigations of Dr. E. V. McCollum and his co-workers, we know that the growth of the osseous system depends on the vitamin D content of the food and the correct calcium-phosphorus ratio. If this is undisturbed; i.e., no relative excess of one or the other, a comparatively small amount of vitamin D is sufficient to guarantee good calcification of the osseous system. However, if there is an excess of one or the other, small quantities of vitamin D do not suffice to prevent severe disturbances of calcification. In other words, if the calcium-phosphorus ratio is disturbed an abundance of vitamin D must be given in order to compensate for the un-

balanced ratio. Otherwise the typical picture of rickets results.

If we consider in this connection the osseous system of an adult for some time on an unbalanced diet, which for instance did not contain calcium enough in proportion to phosphorus, osteoporotic changes develop which manifest themselves in the jaws by a destruction of the trabeculae and an enlargement of the marrow spaces. The same osteoporotic changes of the alveolar process are found if a growing dog is fed with a basal diet and a normal salt mixture, but without the addition of cod liver oil (vitamin D). Roentgenograms show the jaws of such animals to be less dense than those of animals receiving sufficient vitamin D.

If we omit a large part of the calcium in the diet, as well as vitamin D, the typical picture of diffuse *dystrophic* paradentosis develops instead of an osteoporosis. We find typical horizontal and vertical types of atrophy, as well as periodontal dystrophy. These lead clinically to a loosening of the teeth with a tendency to migration, which is especially marked in the region of the anteriors.

The calcium metabolism, therefore, bears a very close relation to the vitamin D content of the food. On the other hand, we know that the calcium metabolism is regulated and controlled by the endocrine system, especially by the parathyroids. According to our experiments, vitamin D represents in a certain way a mediator between the calcium metabolism and the endocrine system. If the osseous system in these cases of paradentosis is primarily involved to a certain extent—which we must believe from our experiments—the question arises in what way the calcium-phosphorus metabolism is changed.

In our blood serum analyses of patients suffering from diffuse dystrophic paradentosis we found an *increased amount of calcium*, as already mentioned. The inorganic phosphorus content is decreased in 50 per cent of the cases and in others it is normal. The calcium-phosphorus quotient, which lies for normal serum between 2.4 and 3.0, is increased in about 50 per cent (of the 25 cases examined).

The examination of the saliva revealed in about 90 per cent of these cases a *decreased calcium amount* with normal or slightly increased phosphorus values. This results in a low calcium-phosphorus quotient; this is exactly the reverse of what we found in the blood. We see, therefore, that we are dealing with a definite disturbance in the potassium-calcium and the calcium-phosphorus quotient in these cases of paradentosis.

Clinically we observe that bone substance is being lost and biochemically we find a hypercalcemia with a frequent relative or absolute lack of phosphorus in the blood serum.

In the mixed resting saliva, however, we find a hypocalcemia and a normal or relatively high phosphorus content.

These findings have carried us one step further in the recognition of these types of paradentosis. They may be interpreted to mean that either an endocrine disturbance, perhaps pluriglandular disturbances, a deficient diet, infectious disease, or other metabolic diseases mobilize calcium salts from the bone and perhaps from the teeth.

which leads to an increase in the amount of calcium in blood serum. This increase of serum calcium in most of the cases is not accompanied by an increase of the blood phosphorus resulting in a relatively high calcium-phosphorus quotient and a low potassium-calcium quotient. Since we find in the mixed saliva of these patients a low calcium content with a relatively high phosphorus content, which is exactly the opposite of what we find in the blood, we must trace this to the factors influencing the secretion or excretion processes in hypercalcemia.

This shifting in the calcium-phosphorus quotient encourages me to define more precisely that type of paradentosis with which the medical and dental professions are so often confronted: *The diffuse dystrophic paradentosis* is characterized clinically by a primary bone disturbance on the basis of an osteopathy with a tendency of the teeth to migration and loosening without inflammatory symptoms. This osteopathy is so slight that no clinical manifestations of disturbance of the general osseous system are to be found. The biochemical aspect is characterized by a high calcium-phosphorus ratio of the blood serum. The total serum calcium amount is increased with a relative or absolute lack of inorganic phosphorus. The potassium-calcium ratio of blood serum is frequently found below normal.

The Report of a Case of Early Hodgkin's Disease Secondarily Infected with a Strain of Pathogenic Monilia *

By Samuel R. Haythorn, M.D., F.A.C.P., George H. Robinson, Ph.D., and Lloyd Johnson, M.D., *Pittsburgh, Pa.*

THE patient concerned in this report was a man 70 years of age who presented an unusual combination of clinical and pathological findings. The diagnosis of Hodgkin's disease was based entirely on the microscopic changes and was not suspected during life or from the gross findings at autopsy. The outstanding features of the case were inflammatory lesions of the lungs and spleen and the isolation of a pathogenic strain of monilia. The unusual lung lesions were found microscopically to be nodules of organizing pneumonia through which numerous large cells of the "Dorothy Reed" type were distributed, and which we interpreted as having been attracted to the site by the irritating influences of the monilia. There were several other unusual circumstances not commonly associated with Hodgkin's disease such as the age of the patient, the atypical blood picture, the absence of enlarged glands and the unusually high fluctuations of the temperature.

*From the William H. Singer Memorial Research Laboratory and the Allegheny General Hospital, Pittsburgh, Pa. Received for publication, September 18, 1931.

Case Report

Abstract of Clinical History

First Admission

Mr. W. A. N., aged 70 years, a farmer, was admitted to the service of Dr. Lloyd W. Johnson on August 15, 1928. There was no family history of neoplasms and the patient's habits were of the best. He was an active farmer, working from twelve to fourteen hours daily until one week before his first admission and then complained chiefly of chronic arthritis.

He was admitted for chills, fever and arthritis. No satisfactory diagnosis was made and he was discharged in two weeks, much improved. All examinations were negative. There were no enlarged glands.

Second Admission

He returned October 2, 1928, with chills and fever, pain in gall-bladder region and arthritis. The fever alternated with chills and the temperature rose daily to 101° or 103°, the pulse going to 110 or more. Toward the last the daily temperature curve was typical of septicemia.

Physical examination showed pyorrhea, a heavy coating of tongue, and slight jaundice. The glands still were not enlarged. Six weeks before death the patient began to cough. Crackling râles were present in the lungs. Ten days before death a definite bronchopneumonia developed. The pain in the upper abdomen was almost unbearable. The patient died December 14, 1928.

The treatment throughout was symptomatic. Several blood transfusions were

made. Potassium iodide was given for four weeks without improvement.

Blood examination on the second admission (10-2-28) showed red blood cells, 3,170,000; white bloods cells, 11,000; hemoglobin, 80%, Sahli; polymorphonuclears, 75%; lymphocytes, 22%; large mononuclears, 3%.

The final blood examination, made on 12-5-28, gave red blood cells, 2,900,000; white blood cells, 14,500; hemoglobin, 64%; polymorphonuclears, 86.5%; lymphocytes, 9%; large mononuclears, 4.5%; eosinophiles, 0, in 200 cells.

The urine was negative. The icterus index, 36 units bilirubin. The Widal test, *B. abortus* and *B. tularense* agglutinations were negative. The Wassermann and Kahn tests were negative. The sputum was negative for tubercle bacilli.

The X-ray verified the arthritis and diffuse infiltration of the lungs.

Clinical Diagnoses: Chronic cholecystitis; arthritis; septicemia due to undetermined cause; icterus; terminal bronchopneumonia and myocarditis.

Abstract of Protocol

The body was that of an emaciated male 170 cm. in length. The skin and scleræ

FIG. 1. Left lung showing Hodgkin's disease nodules and diffuse organizing pneumonia near base.

were distinctly yellow. All of the upper teeth and several of the lower ones were absent. Those remaining were in poor condition. The tongue was heavily furred. There were no skin lesions and no superficial glandular enlargements.

Pericardium: The pericardial sac contained 100 c.c. of bloody fluid. A firm band of adhesions connected the apex of the heart to the parietal pericardium, and there was an area of acute fibrinous exudate on the epicardium.

Heart: Weight 490 Gm. The cavities and valvular orifices were negative; the coronary arteries were sclerosed; one branch of the left coronary being completely obliterated. The myocardium was white and fibrous.

Left Lung: Weight, 355 Gm. The upper lobe was not remarkable. In the lower lobe there were two kinds of nodules, varying in size up to a diameter of 2 cm. Two of the larger ones appeared to be calcified tubercles. The other nodules were numerous and had no distinct borders. Some were firm, white and tinged with red. Others were hard, white, and had excavated centers containing a thick creamy exudate. The lung tissue between the nodules was dry, air containing, and appeared normal. The bronchi were moist, reddened and some contained muco-pus. The peribronchial lymph nodes were enlarged to about 2.5 cm. in diameter, were grayish white in color, and resembled nodes infiltrated by tumor growth.

Right Lung: Weight, 510 Gm. Nodules similar to those in the left lung were present in all three lobes. In the lower lobe was a small area of diffuse consolidation 5 by 3 by 2 cm., and scattered areas of

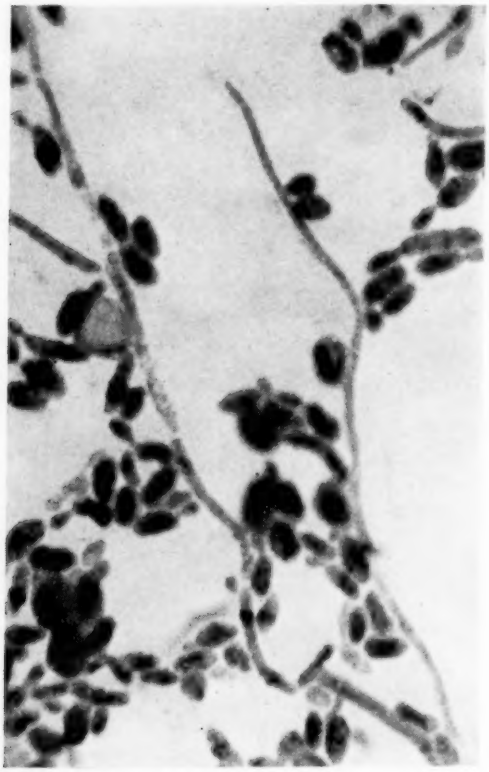


FIG. 2. Smear from active culture of monilia, showing mycelial and budding forms. Oil immersion.

bronchopneumonia. There were also collapse of the posterior portion of the upper lobe and compensatory emphysema of the apex. The bronchi and nodes resembled those of the left lung.

Gastrointestinal tract: There was an acute inflammation of the duodenum and edema of the papilla of Vater. The rest of the gastrointestinal tract was negative.

Liver: Weight, 1590 Gm. In general the liver presented the picture of chronic passive congestion with moderate bile stasis. There were three firm white irregular nodules with sharply scalloped borders and reddened margins. The largest was 2 cm. in diameter and had a cartilage-like center. The gall bladder was distended with thick, sticky, mucoid, reddish-green bile. The mucosa was injected, edematous and inflamed. No stones were present.

Spleen: Weight, 295 Gm. It measured 17 by 9 by 4.5 cm. The capsule was thin and tightly stretched. Pale blotches were apparent beneath it. On section the pulp was a deep, purple color with many creamy white spots.

Kidneys: Both kidneys presented the picture of chronic arteriosclerotic nephritis with retention cysts. The right contained a healing infarct near the upper pole.

The mesenteric and retroperitoneal nodes were somewhat enlarged, white, firm, and infiltrated.

The pancreas, adrenals, prostate, bladder, and testes were negative.

The head was reserved. The joints were not opened.

Principal Diagnosis: General granulomatosis of uncertain cause.

Additional Diagnoses: Acute fibrinous pericarditis with effusion; old pericarditis with adhesions, healed infarct of myocardi-

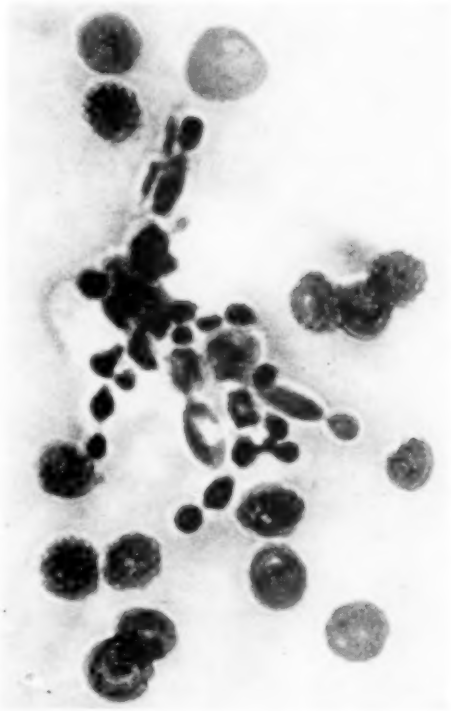


FIG. 3. Smear made from a mixture of monilia and blood. The monilia take the nuclear stains. The preparation shows the difficulty of differentiation between the monilial spores and the nuclei of the leukocytes. The resemblance made the demonstration of monilia in tissues particularly difficult.

um; collapse of right lung with compensatory emphysema; chronic adhesive pleuritis; healed tuberculosis; multiple infarcts of spleen with enlargement; chronic passive congestion of liver; chronic cholecystitis and cholangitis; chronic nephritis; adenomatous hyperplasia of the prostate; general icterus; enlargement of joints.

Post Mortem Bacteriological Report

Cultures were made at autopsy from the heart blood, pericardial fluid, bile, spleen, lungs and peribronchial nodes. All cultures yielded a heavy growth of B. coli. Large organisms, apparently mycelial forms of a fungus, could be seen in the cultures from heart blood, spleen, pericardium and peribronchial lymph nodes. After two weeks' incubation the colon bacilli died out and the fungus which proved to be a strain of monilia was isolated in pure cultures.

The monilia colonies were white and glistening. When less than 24 hours old short arboreal processes extended from the colony. On microscopic examination these processes consisted of branching mycelia with oval spores forming at the ends and nodes. Smears of older colonies revealed only spores with occasionally a shadowy or skeletal remnant of a mycelium. All forms were Gram positive and showed no structural features except an irregular concentration of the nuclear material in some of the spores.

In broth this organism grew with slight granular turbidity which generally settled to the bottom. Acid was produced in dextrose and maltose broth. Lactose, saccharose, mannite and salicin were not affected. It did not give the characteristic yeast odor in broth or upon potato.

Large doses of culture administered intravenously were fatal for rabbits. Subcutaneous inoculation in rabbits and guinea pigs produced abscesses.

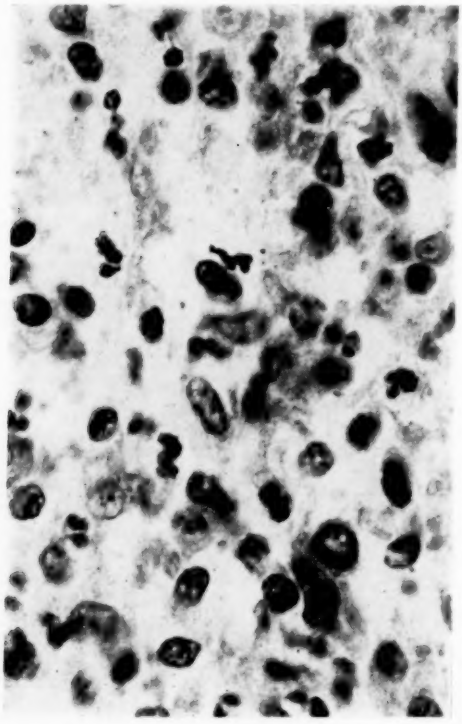


FIG. 4. Photograph to show monilia in lung nodule. Note the group of monilia just above the center of the field. These monilia stood out as red bodies with pyronin and licht grün.

Diagnosis: Monilia (species not determined).

Microscopic Findings

Heart: The myocardium showed fibrous myocarditis.

Lungs: The lung sections showed a diffuse purulent exudate throughout the bronchi and bronchioles. They contained many bacteria and some larger irregular forms resembling monilia. The large cells to be described in the nodules were also seen in the alveolar walls at some distance from the nodules. There were a few areas of organizing pneumonia not associated with nodules.

Several sections of the lung contained well defined nodules, which were discrete, situated beneath the pleura. The margins were sharp and without limiting membranes. The alveoli in the advancing margins of the nodules were filled with fibrinous exudate and were often found lying next to normal air sacs. In the affected areas all structures including bronchioles, blood vessels and alveolar spaces were destroyed by the granulomatous process. Apparently the reaction consisted of a primary fibrinous exudate which spread at the borders and organized at the centers. A typical nodule included one or more small bronchioles in which the epithelium was partially thrown off and partially swollen and adherent. The bronchial submucosa was infiltrated with an exudate of polymorphonuclear leucocytes. Toward the centers of the nodules, all normal landmarks were lost and the mass was made up of interlacing strands of fibrin, newly formed fibroblasts, fibrils, capillaries, infiltrating cells and broken bits of monilia. The monilia were differentiated with difficulty. They were not acid fast. They stained blue with phloxine-methylene blue and with the Gram-Weigert method. In both instances they took the fibrin and

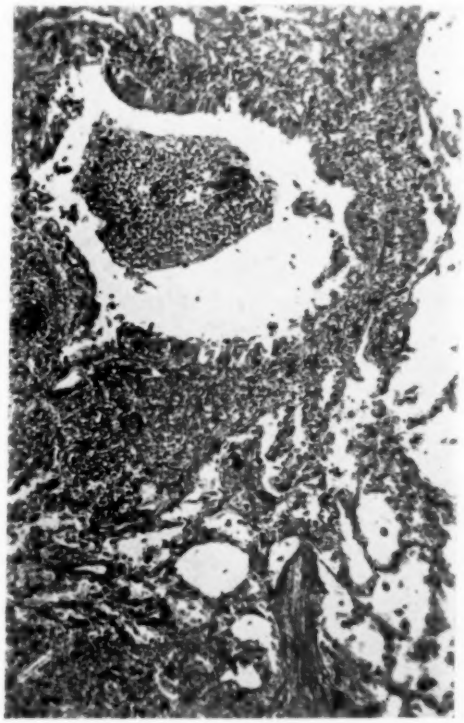


FIG. 5. Photograph of lung showing bronchiole filled with leukocytes and alveoli filled with fibrin undergoing organization.

nuclear stains and could not be differentiated with certainty. By means of Giemsa's stain they could be differentiated from fibrin but not from nuclear particles. At the suggestion of Dr. Baldwin Lucké, pyronin and licht grün were used and a moderate number of red staining bodies which were morphologically monilia were found distributed throughout the lung lesions and bronchioles.

The kinds and relative numbers of inflammatory cells in the nodules varied considerably from field to field. Polymorphonuclear cells were diffusely distributed. Lymphocytes, plasma cells and large mononuclear phagocytes were very common and were the predominating cells in some areas. Some of them contained phagocytosed ovoid monilia, often two or three to a cell. Typical phagocytic foreign body giant cells with from three to ten or more nuclei were numerous and widely distributed. The unusual feature was the presence of many large cells which appeared to be identical with the "Dorothy Reed" cell of Hodgkin's disease. These were large cells with pink cytoplasm, irregular borders, vacuolated nuclei, which often had multiple nucleoli. Some of the cells were in mitosis and some had more than one nucleus. Some of these cells resembled megakaryocytes of the bone marrow.

Liver: In several sections there were portions of nodules, which were identical with those found in Hodgkin's disease.

Spleen: In general the spleen showed congestion with areas of red cells. The white granulomatous areas were essentially infarcts, with borders which were not sharply defined. "Dorothy Reed" cells were numerous in the pulp. Golden pigment-bearing cells and foreign body giant cells completed the picture.

Kidneys: A moderate degree of arteriosclerotic nephritis was present, and one section had an infarct in the later stages of healing. The sclerosis was of the Monckeberg type.

Lymph Nodes: The lymph nodes were replaced by fibrous tissue and presented the usual picture of Hodgkin's disease. The lymph follicles and normal arrangement of the nodes were lost. In some parts the

FIG. 6. Photograph of peribronchial lymph node, presenting the picture of the sarcomatous form of Hodgkin's disease. Note the large cells, fibrosis, and absence of germ centers.

fibrous bands were wide and made up of many collagen fibrils which separated the gland into irregular alveolar spaces, filled with cells. The greatest number of cells were lymphocytes with large, deeply staining nuclei. Among them were many large cells with clear protoplasm, large cart wheel-like nuclei and one or more large nucleoli. Mitotic figures in these cells were numerous. Some were mononuclear and some had two or more nuclei. There was also a fair number of multinucleated giant cells of the foreign body type which presented typical, dark, evenly stained nuclei. In the peribronchial nodes, the giant cells often contained carbon pigment, while large cells which resembled the "Dorothy Reed" cells did not. Spore-like monilia bodies were found.

The pancreas, aorta, adrenals, and other organs showed no lesions attributable to monilia.

Experimental Lesions

Animal inoculations were made to prove the pathogenicity of the monilia. The intravenous injection of rabbits with pure cultures produced death within twenty-four hours. No microscopic studies of this group were made. Rabbits and guinea pigs were inoculated subcutaneously and intraperitoneally. In a week or ten days this group showed abscesses at the site of inoculation and monilia were recovered culturally and were demonstrated in the sections with pyronin and licht grün stains. In animals allowed to live for longer periods the abscesses healed by becoming surrounded by mononuclear leucocytes of the foam-cell type and by encapsulation. Finally, foreign body granulomas were formed containing giant cells filled with mycelial bodies and ovoid forms. Cultures were placed in the nostrils of anesthetized guinea pigs and a diffuse bronchitis

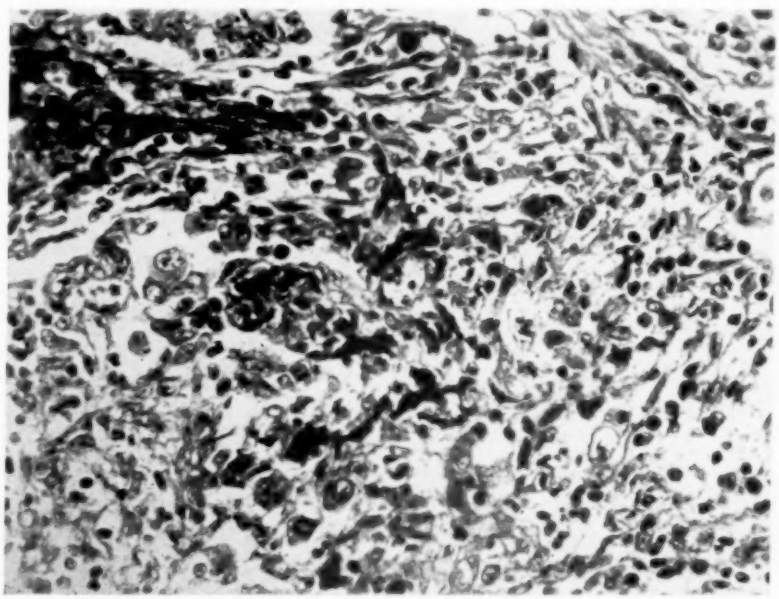


Fig. 7. Higher power photograph of lung to show mononuclear cell type of exudate in nodule. A cell resembling a "Dorothy Reed" cell is present in the right center near the top. The dark staining masses were at first believed to be monilia but took the bluish green stain with Unna's pyronin and licht grün, showing that they were fibrin.

produced. Several of these animals died within two weeks.

Summary and Discussion of Points for and Against Hodgkin's Disease

A. Clinical Findings. The clinical course indicated some unusual condition other than Hodgkin's disease or some overshadowing concurrent infection. Against Hodgkin's disease were the following points. The patient was in his seventy-first year which is far beyond the average age of Hodgkin's disease. Cases have been reported up to the age of seventy-six but the usual age is between twenty and forty and cases over fifty are rare. There were no superficial glandular enlargements. The symptoms and signs pointed to cholecystitis, arthritis, both of which were present, and to some chronic progressive granulomatous lesion in the lungs accompanied by chills and fever. The lung symptoms coincided closely with the reports of pulmonary moniliasis in the tropics and particularly resembled that condition as described by Farrah[1] among tea tasters in Ceylon. References to the reports of sixty-nine instances of pulmonary moniliasis in the United States were found in the literature since 1915. The fever in our case was of the septic type and was higher than that usually found in Hodgkin's disease. The blood picture was atypical. A secondary anemia did develop in the later stages though the continued leukocytosis of about 17,000 with a relative polymorphonuclear leukocytosis of 86.5 per cent and an absence of eosinophils favored acute infection. The patient was under observation for arthritis for six months and was in the hospital for the last ten weeks of his life where he was seen daily by various members of the staff, all experienced in Hodgkin's disease; further, unusually complete laboratory work was done without anyone even so much as considering Hodgkin's disease as a possibility.

B. Bacterial Findings. The organisms recovered are not known to be associated with Hodgkin's disease. *B. coli* and monilia were isolated from the lungs, peribronchial lymph nodes and blood stream. *B. coli* was considered to be a secondary invader. Monilia were unique as an autopsy finding in our experience. They resembled *M. psilosis* though they were not considered identical. There was a heavy fur upon the tongue which could have been the source of a general terminal distribution, though we do not think this likely. We found gram-positive structures in the lung lesions and in some of the bronchioles away from the nodules which we believed to be monilia. The monilia were pathogenic for rats, guinea pigs and rabbits in which they produced chronic abscesses. Smears and cultures of these abscesses were regularly positive for monilia though they could be demonstrated only with the greatest difficulty in the sections, because their morphology, size, and staining reactions varied widely. We considered the monilia the responsible agents for the inflammatory part of the lung lesions, and for the acute lesions in the spleen, but only an accidental association with Hodgkin's disease.

C. Pathologic Findings. The pathologic findings were not characteristic and were confusing. The diagno-

sis of Hodgkin's disease rested on the microscopic changes in the peribronchial nodes and upon the presence of "Dorothy Reed" cells in the lesions of the other organs. In typical Hodgkin's disease the lungs may escape entirely, but in this instance the lesions of the lungs were the outstanding pathological features and included organizing pneumonia, acute and chronic bronchitis, as well as the nodules. Inflammatory changes in the spleen were far more acute than typical Hodgkin's nodules. The question arose as to whether the case was a general moniliasis, Hodgkin's disease, or a combination of the two.

Sections were sent to several laboratories and the opinions of various pathologists were not wholly in agreement. Two reported "Hodgkin's sarcoma". Three reported Hodgkin's disease with unusual inflammatory reactions in the lung not typical of Hodgkin's disease. One said that the lymph node lesions would probably be diagnosed Hodgkin's disease in most laboratories, but that the lung lesions could be accounted for on a purely inflammatory basis. Another made a diagnosis of Hodgkin's disease, though he qualified the statement in that he had seen the same large cells in avian tuberculosis and believed them to be megakaryocytes. One said that the large cells were present in a case of moniliasis of bone which he had studied.

After the demonstration of the monilia-like bodies in the lungs and spleen by means of the pyronin and licht grün stains, we made the final diagnosis as it appears in the title of this report.

Conclusion

A case of early Hodgkin's disease is described which appeared to be secondarily infected with a strain of pathogenic monilia. The reaction in the infected areas, as well as the Hodgkin's nodules contained the typical "Dorothy Reed" cells.

This finding suggested that these cells are wandering cells which may respond to inflammatory stimuli outside of the Hodgkin's nodules, just as other wandering cells and blood elements are capable of doing.

REFERENCE

[1]Farah, N.: Observations on Castellani's bronchomoniliasis, with report of a case with pneumonic onset and a peculiar clinical aspect, Jr. Trop. Med., 1923, xxvi, 1-5.

Spotted Fever Immunization:

Results and Recommendations*

By Noxon Toomey, M.D., F.A.C.P., *Palmyra, Mo.*

CONSEQUENT upon a widening area of distribution and upon the increasing population within the areas that have become endemically affected, the spotted fever of the Rocky Mountains has become of enhancing importance as a public health problem.[218, 223] Of this fact, cognisance has been taken by state and local health officers, by regional and inter-state conferences, by private practitioners, and by the increasing coöperation of the Federal Government. The coöperation of the latter has taken the form chiefly of conducting epidemiologic and ecologic studies in the field, of carrying out laboratory investigations on the virus, and of the manufacture, in annually increasing quantities, of a preventive vaccine of proven, and we might add, great value.[209, 225]

The vaccine, as originated by R. R. Spencer and R. R. Parker has an important place in any control program, but is particularly necessary for use in localities where tick control measures can not be conducted economically, due either to the character of the terrain, the sparseness of the population, or the very occasional character of the menace from spotted fever. Where, however, it has been found profitable to maintain tick control procedures, there is not yet justification for diminishing the tick control activities because of the recent introduction of a preventive vaccine.[224]

This paper will be limited to a study of the production, distribution, and efficacy of the spotted fever vaccine as originated by R. R. Spencer and R. R. Parker; the value of the vaccine as compared with other spotted fever control measures being given only incidental consideration inasmuch as this aspect has lately been elsewhere considered in detail by the author.[231]

The need for a preventive serum or vaccine was early apparent in the study of possible prophylactic measures against spotted fever, as the disease is of great economic importance in the areas where it is most prevalent; as also in areas where it is of (consistently) great virulence.[36,47,97] P. G. Heinemann and J. J. Moore[76,84] attacked the problem from the aspect of passive immunity. They showed that passive immunization offered virtually no prospect for effective prevention or therapy. It was H. T. Ricketts[49,56,75] and associates[61,69], and later Noguchi[142,143,144] who conducted the first studies on active immunization against spotted fever. Subsequent studies of related nature were reported by Conner[147,148], by Breinl[163], by Kuczynski[166], and by Otto[177]. It was not, however, until the experiments of R. R. Spencer and R.

*Received for publication, March 5, 1932.

R. Parker resulted in the production of an attenuated virus, in sufficient concentration, that a practical vaccine became available.[150,153] This vaccine was first released for distribution in 1925.

The Nature of the Vaccine

The vaccine is the spotted fever virus obtained from infected ticks ("tick virus") rather than from the blood of infected animals ("blood virus"); its virulency is attenuated by chemical means. It is standardized for approximate potency by biologic (guinea pig) assay. Each dose (2 c.c.) equals the attenuation of approximately 20,000 minimum infectious doses for a guinea pig. Two such doses at five day intervals have constituted the standard course, which requires being repeated annually.

Although most vaccines are prepared by heating the organisms to 56° C. it has been found necessary to obtain attenuation by means of a chemical, as the protective quality of spotted fever virus is entirely destroyed at the temperature of 56° C.

Manufacture of the Vaccine

Wild adult ticks, collected in the field, are permitted to feed on infected guinea pigs after the onset of the fever, placing about 75 ticks in a wire gauze capsule fastened to each animal. After two days of feeding the ticks are removed and placed at room temperature over moist sand, where they may be kept for several months. Before being used for making vaccine these ticks are again fed, this time on normal animals, for five or six days. This second feeding produces a tremendous increase in the number of minimal infectious doses of the virus per tick. For routine purposes it is not necessary to determine this dosage by the graded injections of the live tick-virus suspensions, as was formerly done.

The partly engorged ticks (male and female) are now ground in a mechanically operated porcelain mortar and pestle with fine quartz sand and a small quantity of physiological salt solution which contains 1.6 per cent phenol and 0.4 per cent formalin. After thorough grinding the whole mass is transferred to a large stock bottle, and an additional amount of the salt solution and preservative is added until the concentration reaches, but does not exceed, four ticks per cubic centimeter. After standing for 48 hours, during which time the preservatives will precipitate most of the protein, an equal volume of physiological salt solution is added. This dilutes the preservatives to 0.8 per cent phenol and 0.2 per cent formalin. At this stage the material is kept for seven days at room temperature. This has been found a sufficient period to kill most extraneous organisms, including sporebearers.

The suspension is then diluted once more by again adding an equal volume of salt solution. This final dilution will contain 0.4 per cent phenol, 0.1 per cent formalin, and the killed virus equivalent of one tick per cubic centimeter. The sand, chitin, and precipitated protein is now removed by centrifugation and the remaining clear amber-colored supernatant fluid is ready for the final containers. Occasionally some precipitate forms afterwards. This can be disregarded, for it does no harm when injected, and besides has protective value. In fact, the discarded heavy precipitates from potent lots may be combined and resuspended in sterile salt solution, again cleared by centrifugation, and the clear supernatant fluid still found to possess high protective value. A number of such lots have been so made and used in human vaccination.[199]

Test for Potency and Sterility. Each lot is tested for potency by inoculating six guinea pigs subcutaneously with one cubic centimeter each. After twelve days the animals are given intraperitoneally a test dose of one cubic centimeter of guinea pig blood virus. If four of the six animals do not show symptoms of spotted fever the vaccine is considered suitable for human use. An arbitrary standard of potency of this kind admits the operation of several variables. The potency of any two lots of vaccine is only approximately the same.

Sterility tests are made in accordance

with the hygienic laboratory procedure for biologic products.

Keeping Quality. The vaccine is fairly stable at ice box and room temperature. Ice box preserved vaccine protected guinea pigs invariably up to 200 days and 6 out of 9 pigs at 576 to 597 days. Vaccine kept at room temperature protected 8 of 9 pigs up to 108 days and one-half of 10 pigs at 215 days, the remainder dying of spotted fever.

Distribution of the Vaccine

The vaccine is produced solely by the U. S. Public Health Service at Hamilton, Montana. It is distributed to physicians without charge and it is expected that only a nominal charge will be made for administering the vaccine. Application for the vaccine should be made to the Officer in Charge, U. S. Public Health Service, Hamilton, Montana.

Each year there has been an increasing demand for the vaccine. The heaviest calls are from Montana, Wyoming, Idaho, and Oregon, the last named state using the most in 1930. There is a moderate demand from South Dakota, Nebraska, Colorado, Nevada, and Washington.

The amounts that have been distributed are as follows:

Year	C.C.	Number of Doses	Number of Courses
1925	372	186	93
1926	3,412	1,706	856
1927	6,284	3,064*	1,532
1928	6,500	3,250	1,625
1929	16,600	7,786	3,893
1930	32,000	16,000	8,000
1931	64,000	32,000	16,000

*Includes 312 doses at 2.5 c.c. per dose.

Method of Administration

Equally good protection has been effected by the subcutaneous, intravenous, intramuscular, and intraperitoneal routes, the latter employed in guinea pigs only. Ordinarily the vaccine is administered subcutaneously. Attempts to vaccinate animals by forcing them to swallow the vaccine have produced immunity in only a few instances, and failed in the great majority of cases.

Reactions

Less than five per cent of four thousand persons have complained of constitutional symptoms. These have included malaise, slight fever, nausea, and aching joints or muscles. Protein reactions with urticaria and edema have occurred in about one per cent of those vaccinated, the symptoms usually appearing very shortly or within a few hours after the injection, but in one instance were delayed ten days. The symptoms last from a few hours to several days, but in one man the urticarial rash persisted somewhat for nine months, finally disappearing following infection with spotted fever. About one-half of those who have reacted after the first injection do not do so on subsequent injections, whereas a few react more violently. Marked collapse occurred in one person who, the next day, felt normal except for weakness.[201]

Local reactions have mostly been inconsequential and limited usually to local redness, swelling and itching about the site of injection. Swelling sometimes extends below the elbow and occasionally to the hand. Itching, the most common complaint, either disappears or becomes scarcely noticeable in persons who have been vaccinated several times.

Duration of Immunity

Data from the Bitter Root Valley test indicate that the duration of pro-

tection in the average individual does not exceed one tick season. The period varies in individuals, however, and for some may be quite short. Vaccination annually is therefore desirable.

While effective immunity does not last longer than one year, there is evidence that a residual immunity persists for a much longer time.

Populations Immunized

Immunization has included the vaccination of three accurately controlled experimental groups, and a dispersive, not accurately controlled distribution of the vaccine. The general distribution, not available for accurate comparative statistics was as follows:

In	No. of Individuals to Jan. 1, 1930	No. of Individuals to Jan. 1, 1932 (Approximately)
Montana (excluding Bitter Root Valley test group)	401	2,600
(including test group)	(3,231)	(7,100)
Idaho (excluding test group)	203	1,400
(including test group)	(396)	(1,593)
Wyoming	863	2,900
Oregon	30	3,300
Nevada	5	300
Colorado	3	275
Utah, Dakotas and Nebraska	2	275
Washington and California	0	250
General distribution	1,507	8,300
Total distribution	4,530	16,000

The three test or controlled groups were the following: the U. S. Public Health Service workers (including state control employees); the Idaho Test Group, and the Bitter Root Valley Test Group. The Idaho Test Group included 94 persons in 1926 and 99 in 1927 (none thereafter), a second annual vaccination not being offered in 1927 to those vaccinated in 1926. The number of inoculations administered to the Public Health Service (including state control) employees is included in the following statistics concerning the Bitter Root Valley Group.

The following table (table I) shows the number of individuals who, in each year, had received the number of vaccinations and revaccinations as indicated by the integers on the course line.

Table I

COURSES RECEIVED:	1	2	3	4	5	6	7	TOTAL
1925	34							34
1926	624	30						654
1927	846	339	112					1,296
1928	1,469	430	141	11				2,051
1929	2,067	491	191	71	10			2,830
1930	2,550	555	257	143	64	9		3,578
1931*	2,720	800	550	265	150	10	5	4,500

*Estimate by the author, official records not yet compiled for publication.

Results

From the results of a two year test (1926 and 1927) made in southern Idaho (Snake River Valley) against the mildest type of the disease, and another test against the most virulent type, which has been in progress for seven years in the Bitter Root Valley, the following conclusions are justified —that against the milder types of infection the vaccine usually affords full or nearly full protection, while against the highly virulent type the degree of protection is usually sufficient to cause a marked amelioration of the customary very severe symptoms, and to predispose to the recovery of most cases.

In southern Idaho infection is very prevalent among persons handling

sheep on the range, and the test was therefore confined to that industry. During the two seasons of 1926 and 1927, 193 sheep herders were vaccinated, and 364 non-immunes served as controls. A single case only occurred among the vaccinated men (1 in 193). This man had refused the second injection. Among the 364 control individuals there were 22 cases, or one in every 16.55 men.

The Bitter Root Valley case mortality for the twelve years, 1917 to 1928, was 53 deaths out of 69 cases, a rate of 76.81 per cent. In six of these twelve years the mortality for adults was 100 per cent. During the period of the four years under consideration (1925-1929) there were, including the non-vaccinated control group, a total of 18 cases with 15 deaths, a case mortality rate of 83.3 per cent, among the non-vaccinated persons living in the Bitter Root Valley.

The results of the test against the malignant Bitter Root Valley strain yield the following statistics for the period 1925 to 1931, inclusive:

	Vaccinated Group	Non-vaccinated, Control Group
Number of individuals in group	3,578	about 8,700
Approximate ratio to whole population	30%	70%
Number of cases in group	16	30
Case incidence	1:223*	1:290
Died	2	22
Death rate	12.5%	73.32%
(Parker-Spencer series	9.09%	90.91%

*The slightly greater incidence rate in the vaccinated group was due to the fact that vaccination was first carried out to proportionately greater degree in a "well defined dangerous zone on the west side of the valley", where of 1,208 persons, 496 were vaccinated, letting the remainder, 712 in number, serve as controls. Considering only the group of 1208 in the dangerous zone on the west side of the valley, there were during the four years (1926-1929) three cases (1 in 165) among the members of the vaccinated group, none of which was fatal, while there were nine cases (1 in 79) among the non-vaccinated group, seven of which proved fatal, a case mortality rate of 77.7 per cent.

A composition of the Public Health Service (Group A) cases, seven in number (with one death), the Bitter Root Valley cases, 16 in number (with two deaths) and the experience of Dr. E. L. Jewell with two cases (both recovered) each with the equally fatal Kirby Creek strain of spotted fever, gives a total of only three deaths in twenty-five cases of almost fatal virulency, a mortality rate of 12 per cent against the twelve year average of 85 per cent.

Parker and Spencer, writing of their initial series, have been able to say "Considering only adult cases in the Bitter Root Valley as a whole, the recovery of 10 of 11 vaccinated adults, 7 of Group A and 4 of Group B (90.91 per cent recovery) during the four year test period offers vivid contrast, first with the death of 10 of 11 non-vaccinated adults (90.91 per cent mortality) during the same period, and second, with death of 9 of every 11 non-vaccinated adult cases (84.91 per cent mortality) during the past twelve years."[201]

Prospects

Having passed the experimental stage, the prospects for the adequate employment of the vaccine have to do

with problems of distribution, and of coördinating the use of the vaccine with other control measures, according to the relative economic positions of the measures available. Maximum distribution requires suitable publicity and organization of distributing channels—matters of routine.

The evaluation of the vaccine's economic position is not definitely established, there appearing to be a tendency to undervalue it (compared with other measures) even by those reasonably conversant with the situation. This we believe is a great mistake.

The limited supply, the high cost of manufacture, the disposition of many persons to refuse to submit to any sort of vaccination, the necessity for annual reinoculations, and the popular appeal of other more visibly tangible control measures, such as tick destruction and rodent destruction, all serve to restrict the use of the vaccine to a greater degree than they should.

While it is evident that other control measures can not be diminished the slightest, in areas of great malignancy or tick concentration, on account of the introduction of the vaccine, the great fallibility of these measures renders imperative the systematic use of the vaccine in all dangerous areas, despite the additional cost. In areas of lesser danger the use of the vaccine is equally imperative, as in most such localities the liberal use of tick destruction and rodent destruction measures are economically infeasible. Particularly requiring the vaccine are transient visitors to dangerous areas, and residents of remote or sparsely settled localities in the infected areas. It is particularly the latter class of persons that present serious problems in the matter of distribution.

In final analysis it is apparent that the prospects for the use of the vaccine are predominatingly in the hands of the medical men serving in the localities affected; if they energetically sponsor the use of the vaccine they will be supported by the proper persons for obtaining the necessary publicity; if they are negligent the popular appeal will eventually foster an increasing use of the vaccine, but never perhaps to a sufficient degree unless actively supported by the medical profession. Certainly, however, there is no reason to infer that physicians will be remiss in this matter, as the initial response of the profession has been exceedingly gratifying. Nevertheless, to facilitate distribution, various regional organizations and standards need to be created; these are matters of administration, largely being developed at the present time, and will be dealt with as recommendations.

Recommendations

Current problems have to do with methods of manufacture and standardization, means of distribution, educational programs, and plans of inoculation.

The progressively increasing demand for the vaccine will undoubtedly be met adequately by the U. S. Public Health Service for years to come. It may, however, become necessary to require some reallocations in the manner of defraying the cost of manufacture, as the production of the vaccine is exceptionally costly due to the high labor charge for field work in obtaining the ticks, and for the laboratory work

needed to infect them and rear them. Methods of manufacture are, however, being studied from the aspect of reducing unit cost and of increasing potency. A better method for assaying and standardizing potency is desirable.

Distribution through the medical profession should continue as the main avenue of release. In controlled areas and other highly malignant localities, the vaccination should be under the immediate supervision of the statistician in charge. For reaching men on remote sheep ranges, the state sheep inspectors, veterinarians, and other intelligent persons of the locality should be trained to give the vaccine and to keep the records.

As maximum distribution can not be obtained without persistent publicity of the proper sort, it is recommended that newspaper editors, ministers, school teachers, district supervisors, and educators in the higher grades be officially requested to publish the facts concerning spotted fever vaccination, and to give such information of local interest as will facilitate obtaining the inoculations. For this publicity the school and civic exercises of Washington's birthday should be utilized systematically to the end that the date of February 22 shall become firmly associated in the public mind with the need for obtaining the first of the year's spotted fever inoculations. Similarly in areas of great malignancy the same custom should also become identified with May Day, May 1st, for the single mid-season injection. On the other hand, in areas where one injection of the year is the optimum dosage, this fact should be made known to relieve the public mind and to discourage the needless waste of the vaccine.

Regarding dosage and plan of administration, in view of the need of economy and maximum general efficiency, it is recognized that collectively better results will be obtained by so employing the vaccine as to depart from the present standard dosage (two injections of 2 c.c. each, at five day intervals) wherever local requirements, particularly the greater or less local virulency of the disease, indicate the advisability of establishing an optimum dosage for the locality concerned. Thus a single mid-season injection (about May 1st) in addition to two pre-season injections, is decidedly to be recommended for persons exposed in areas of great malignancy. On the other hand, in certain localities a single annual injection of 2.5 c.c., before the commencement of the tick season, should be considered optimal, according to local conditions. In areas of intermediate virulence the optimum dosage appears to consist of two injections of 2 c.c. each, or possibly the first of 1.5 c.c. and the second of 2.5 c.c., the interval of five days being permissibly lengthened to seven days where local conditions seem to make the latter interval more feasible.

Regarding organization of the distributing channels it is recommendable that state health boards shall (to assist them and the Federal authorities) appoint non-salaried, resident district supervisors among the regular medical practitioners of their State, with view to surveying local requirements, obtaining and supervising proper publicity, keeping records, rendering reports, and otherwise assisting in the

distribution of the vaccine, with consideration to apportioning it where it is most needed.

Summary

Six years' experience with the Spencer-Parker spotted fever vaccine, a chemically attenuated form of the virus, has demonstrated it, by several controlled experiments, to be of great and dependable value in preventing the occurrence of the mild type of spotted fever, and of great value in mitigating the severity of the highly fatal type of the disease, the mortality of the latter being reduced from the twelve year average of eighty-five per cent to approximately ten per cent (nine to twelve per cent).

As the protective action of the vaccine lasts only one season (four to twelve months), annual reinoculations are necessary before the commencement of each tick season. Since the introduction of the vaccine in 1925 to the year 1931, inclusive, between 25,000 and 30,000 persons have been vaccinated; and many of them revaccinated annually from two to six times.

The demonstrated value of the vaccine, and the great need for it in endemic areas, has created an increasing demand for it from the medical profession and the laity, a demand that will continue to be met gratis by the U. S. Public Health Service Laboratory at Helena, Montana, despite unusual difficulties of manufacture and distribution.

While it is recognized that tick destruction and rodent control measures can not be safely diminished on account of the introduction of the vaccine, it is of great importance that the vaccine be used adequately and systematically in all endemic areas, as in most areas it is the only preventive measure available that is both dependable and economically feasible. To effect better distribution and economy, several recommendations are made concerning organization, publicity, and modification of dosage with respect to local requirements, according to the virulency of the local strain.

BIBLIOGRAPHY

[36]Ricketts, H. T.: A summary of investigations of the nature and means of transmission of Rocky Mountain spotted fever, Trans. Chicago Path. Soc., 1907, vii, 73-82.

[47]Ricketts, H. T.: Recent studies of Rocky Mountain spotted fever in Montana and Idaho, Med. Sentinel, 1908, xvi, 688-697.

[48]Tuttle, T. D.: Indications for state control of Rocky Mountain tick fever, Med. Sentinel, 1908, xvi, 697, 704.

[49]Ricketts, H. T., and Gomez, L.: Studies on immunity in Rocky Mountain spotted fever, Jr. Infect. Dis., 1908, v, 221-244.

[56]Ricketts, H. T.: Some aspects of Rocky Mountain spotted fever as shown by recent investigations, Med. Rec., 1909, lxxvi, 843-855.

[61]Gomez, L.: Spotted fever in the rabbit, Jr. Infect. Dis., 1909, vi, 383-386.

[69]Davis, B. F., and Peterson, W. F.: Complement deviation in Rocky Mountain spotted fever, Jr. Infect. Dis., 1911, viii, 330-338.

[75]Davis, B. F.: Unfinished experiments of Dr. Howard T. Ricketts on Rocky Mountain spotted fever. In Contrib. to Med. Sci. by H. T. Ricketts, Univ. of Chicago, 1911, 409-418.

[76]Heinemann, P. J., and Moore, J. J.: The production and concentration of a serum for Rocky Mountain spotted

fever. Preliminary note, Jr. Am. Med. Assoc., 1911, lvii, 198.

[84]Heinemann, P. J., and Moore, J. J.: Experimental therapy of Rocky Mountain spotted fever, Jr. Infect. Dis., 1912, x, 294-304.

[97]Fricks, L. D.: Rocky Mountain spotted fever. A report of laboratory investigations of the virus, Pub. Health Rep., U. S. Pub. Health Serv., 1916, xxxi, 516-521.

[142]Noguchi, H.: Prophylactic inoculation against Rocky Mountain spotted fever, Sp. Bull. No. 26, Montana St. Bd. Health, 1923, 44-47.

[143]Noguchi, H.: Immunity studies of Rocky Mountain spotted fever, Jr. Exper. Med., 1923, xxxvii, 383-394; xxxviii, 605-626.

[144]Noguchi, H.: Experimental prophylactic inoculation against Rocky Mountain spotted fever, Northwest Med., 1923, xxii, 301-303.

[147]Conner, C. L.: Quantitative peculiarities of mixtures of the virus and immune serum of Rocky Mountain spotted fever, Jr. Med. Research, 1924, xliv, 317-328.

[148]Conner, C. L.: Immunity in Rocky Mountain spotted fever, Jr. Immunol., 1924, ix, 269-289.

[150]Spencer, R. R., and Parker, R. R.: Experimental studies on tick virus, U. S. Pub. Health Rep., 1924, xxxix, 3027-3040.

[153]Spencer, R. R., and Parker, R. R.: Vaccination of monkeys and man, U. S. Pub. Health Rep., 1925, xl, 2159-2167.

[163]Breini, F.: Untersuchungen über die Immunität bei Rocky Mountain spotted fever, Ztschr. f. Immunitätsforsch., 1926, xlvi, 123-136.

[166]Kuczynski, M. H., and Brandt, Elizabeth: Neue äetiologische und pathogenetische Untersuchungen in der "Rickettsiengruppe" (Fleckfieber und der Rocky Mountain Spotted Fever), Krankheitsforschung, 1926, iii, 26-74.

[177]Otto, R.: Fleckfieber und amerikanisches Felsengebirgsfieber, Centrlbl. f. Bakterol., etc., Abt. Orig., 1928, v, 106, 279-291.

[199]Spencer, R. R., and Parker, R. R.: Improved method of manufacture of the vaccine and a study of its properties, Hygienic Lab. Bull. No. 154, Wash., D. C., 1930, Pp. 63-72.

[201]Parker, R. R., and Spencer, R. R.: Results of four years human vaccination, Hygienic Lab. Bull. No. 154, Wash., D. C., 1930, Pp. 72-103.

[205]Weigl, R.: Behavior of virus of Rocky Mountain spotted fever in body of mouse. Comp. rend. de soc. de biol., 1930, ciii, 823-826.

[209]Parker, R. R.: Present status of the use of public health vaccine for Rocky Mountain spotted fever, Eighth Bien. Rep. Montana St. Bd. Entomol., 1931, Pp. 36-38.

[218]Dyer, R. E.; Badger, L. F., and Rumreich, A.: Rocky Mountain spotted fever (eastern type). Transmission by the American dog tick (*Dermacentor variabilis*), U. S. Pub. Health Rep., 1931, xlvi, 1403-1413.

[223]Kemp, Hardy A., and Grigsby, C. M.: The occurrence and identification of an infection of the Rocky Mountain spotted fever type in Texas, Texas State Jr. Med., 1931, xxviii, 395-398.

[225]Spencer, R. R.: Expansion of investigation on tick borne diseases by the U. S. Public Health Service. Pub. Health Rep., 1931, vlvi, 2097-2101.

[231]Toomey, Noxon: Control of the tick borne diseases; methods and economics, Ann. Int. Med., 1932, v.

Gastric Secretion–The Electrolytes before and Their Changes at Various Periods after Histamine Stimulation*†

By Lay Martin, B.S., M.D., F.A.C.P., With the Assistance of Morten Morganstern, M.D., and M. L. Carroll, A.B., *Baltimore, Md.*

Introduction

THE institution of hypodermic injections of histamine as a gastric stimulant, has enabled investigators to obtain undiluted gastric juice with much more facility than previously; no corrections have to be made for dilution by an alcohol meal.

Gamble and McIver[1] determined the amount of fixed base in a Pavlov pouch from the fundic end of the stomach. They found a fairly constant level of Cl^1 but a varying amount of base. The level was low on a meal diet, and high on a fasting stomach. The gastric Cl^1 value (158 c.c. 0.1 N per 100 c.c.) is near the total fixed base concentration in blood plasma.

In a series of interesting and well-controlled experiments, MacLean and Griffiths[2] showed that the introduction of acetic acid, hydrochloric acid, and sodium acid sulphate into the stomach will prevent the secretion of hydrochloric acid until enough neutral chloride has been secreted to dilute the gastric contents to 0.2 per cent hydrochloric acid or below. Then hydrochloric acid is secreted. The total chloride soon reaches a level (0.11-0.12 N) and remains so, as if "the combined efforts of emptying and secreting tend to adjust the concentration of Cl^1 to a normal maximum level of 0.11-0.12 N". They believe that "secretion of HCl by the gastric glands is a self-limiting process and after its duty is fulfilled the chlorine is kept level by the secretion through the gastric glands of neutral chlorides".

MacLean and Griffiths[3] were also able to show that dogs having a Pavlov pouch behave in regard to hydrochloric acid and chloride secretion in exactly the same way as normal man: an initial rise in acid, then a fall and concomitantly an increase in neutral chlorides; also, that the total chloride in the pouches remains about constant during secretion. They feel that their work definitely rules out the theory of alkalinization of gastric juice by duodenal regurgitation, which was advanced by Boldyreff[4] in 1915.

In a former experiment, these same investigators[5] determined, by a very delicate method, the amount of carbon dioxide in various specimens of gastric

*From the Gastro-Intestinal and Chemical Divisions of the Department of Medicine of the Johns Hopkins University.

†Delivered in part before the Baltimore Meeting of the American College of Physicians, March 23, 1931.

juice. Only when bile was present were they able to demonstrate an increased amount of carbon dioxide. Furthermore, the hydrochloric acid curve showed the normal rise and fall whether carbon dioxide was present or absent.

On single test specimens of gastric juice, the total bases, the total chlorides, the free hydrochloric acid, and the phosphates were determined by Bulger, Stroud and Heideman.[6] The fasting juice was compared with the secretion stimulated by drink (400 c.c. of water containing 1 c.c. of phenolsulphonphthalein solution). In this way the dilution was corrected. The authors showed that very little change occurred in the total chlorides, but that during secretion the total base fell in proportion to the increase of acid. They believe that the chlorine ions and water leave the blood in about the same concentration as that found in the serum. There appears to be a definite change in the phosphate content of the human gastric juice which is inversely proportional to the content of HCl. Specimens with a phosphorus content as high as 11.17 mg. per cent were found in cases of achlorhydria. Gastric juice with a high HCl content averaged about 4.5 mg. per cent of phosphorus.

Polland, Roberts, and Bloomfield[7] also studied the chloride, base and nitrogen curves before and after histamine stimulation. They found that the increase in titratable acidity is due to the greater increase in output of chloride over base; also, that nitrogen is present, and that it varies in proportion to the base.

In six cases of anacidity following histamine stimulation, Bloomfield, Roberts and Polland[8] found chlorides, bases, and nitrogen in the normal concentration. As the volume of secretion was quite low, the total amount of the substances was naturally much below the average normal.

It seemed of interest to know whether more information could be added to these investigations, and furthermore to ascertain what changes, if any, took place in the blood and urine during the phases of gastric secretion. This part of the investigation will be presented separately.

Method

The one hundred and sixteen individuals investigated were in the great majority from the Gastro-intestinal Dispensary of the Johns Hopkins Hospital. They presented a multiplicity of complaints and sicknesses and they represented a cross-section of the usual number of admissions. A few estimations were made on patients in the medical and surgical wards; these were selected cases. Complete analyses were made on ninety of these 116 patients and the results are recorded below.

The individuals to be investigated reported to the clinic after fasting for 15 hours. A duodenal tube was passed and its position was seen, by fluoroscopy, to be just beyond the dependant portion of the stomach. All patients were cautioned not to swallow saliva. After the removal of the entire fasting contents, each patient was given histamine (ergamine acid phosphate) hypodermically, 0.005 mg. per pound of body weight. Constant drainage was instituted and the total gastric

secretion was collected and separated into three one-half hour periods.

The hydrogen ion concentration was determined by the colorimetric method, using Clark's standards and indicators.[9] Titratable acidity was determined by the standard method using dimethyl-amino-azobenzene and phenolphthalein as indicators; a definite canary yellow color was taken as the end-point of the former indicator and the first permanent pink as that of the latter. Total chlorides were determined by the method of Van Slyke,[10] total bases by the method of Stadie and Ross,[11] inorganic orthophosphates by the method of Benedict and Theis,[12] CO_2 content by the method of Van Slyke and Cullen[13] and trypsin by the author's method.[14]

Observations

For clearness of description the material has been divided as follows:

(a) Those individuals who secrete hydrochloric acid after histamine stimulation:

Group I includes cases which contain free hydrochloric acid in the fasting or resting gastric juice. See table I.*

Group II includes cases which contain no free hydrchloric acid in the fasting juice. See table II.

(b) Those individuals who secrete no hydrochloric acid before or after histamine stimulation:

Group III includes cases which have a gastric juice with a pH between 3.0 and 8.0, the achlorhydrias. See table III.

*To facilitate reading, the figures, graphs and tables have been placed at the end of the article.

Volume

The amount of resting or fasting juice varies within wide limits: Groups I and II from 0 to 190 c.c.; the achlorhydrias, Group III, from 0 to 95 c.c. After histamine stimulation there was almost always a rapid production of gastric juice in the acid producing cases. The amount collected in comparable periods, however, varied within wide limits; the period in which the greatest amount was to be collected, could not be predicted, but usually the maximum was to be found in the first half-hour with decreasing amounts in the second and third. With the production of a large amount of material the consistency became quite limpid, clear and of high titratable acidity. There were cases, however, in which a high titratable acidity was associated with a small volume of thick, mucoid material.

In the cases of achlorhydria, it was quite unusual to collect large amounts. In fact, it was often difficult to obtain sufficient material for the complete analysis. During the various periods it was rare to obtain more than that found in the fasting juice.

Total Chlorides

Chlorides were found in the gastric juice of all patients investigated. The amounts varied within wide limits and in relation to the type of secretion.

The fasting juice of the 25 cases in Group I, hydrochloric acid in all specimens, contained total chlorides between the limits of 88 and 143 milliequivalents per liter, an average secretion of 110. Following histamine stimulation these cases had an increased content in all but four of the

cases, at times rising to a level of 150 to 158 meq.,* with a general average of 127. Usually there was a slight decrease in amount towards the end of secretion. There was, however, much less variation in the chloride content than in the acidity as will be shown later.

The chloride content of the acid free fasting juice of the 21 individuals of Group II was found to be within lower limits, 58 to 113 meq. and averaged 91. After histamine stimulation, an increase similar to that in the group above was noted and although at times the highest chloride content was equal to Group I, the general average was lower, 114 meq. Here the small increase in chlorides after stimulation in comparison to the corresponding acid rise was even more noticeable.

The chloride content of the fasting juice of the 44 cases in Group III who were unable to secrete free hydrochloric acid in any specimen, was found between the limits of 37 and 115 meq., with an average of 81. After stimulation, there was at times an increase and at other times a decrease in the chloride content; in an exceptional instance the amount rose from 108 to 138 meq.; in many cases there was but little change.

The average amounts of the chlorides of the specimens of the three groups have been charted in figure 1 to show the amounts found before and after stimulation. The difference in the levels of the three curves is quite striking.

The cases of Group III, the achlorhydrias, have been separated into four main subdivisions determined by clinical diagnosis. The subdivisions selected were organic disease of the stomach including carcinoma of the stomach and one case of questionable syphilis, marked nephritis with retention of non-protein nitrogen products, pernicious anemia, and benign achylias. These are shown in figure 2. A study of the figure reveals the following interesting points:

1. In the group of benign achlorhydrias, there is a general trend towards a high percentage of chlorides in the gastric juice. The only exceptions to this are Case no. 125, an apparently healthy house officer; Case no. 121, dementia precox; and Case no. 124, an old colored woman. In this group it is clearly seen that there was no fixation of secretion concentration of the salts.
2. The cases of pernicious anemia are able to secrete salts through a wide range of concentration.
3. In the severe nephritics the secretion of chlorides in the gastric juice is at the same high level noted in the benign achlorhydrias. The number of cases is too small to draw any conclusion from the small range of concentration strength from specimen to specimen.
4. The most important finding in the cases of organic disease is that the great majority of these cases secreted a gastric juice having a low salt content. It is also interesting to note that half of these patients were able to vary the chloride secretion concentration through as large a range as

*Hereafter meq. is used as an abbreviation of milliequivalents per liter.

the majority of the benign achlorhydrias. The latter group, however, secreted at a higher level as noted above.

Acidity

Michaelis[15] has shown that all the free hydrochloric acid of the gastric juice has been neutralized when the juice is titrated with alkalies to pH 2.9. This end-point may be recognized (when dimethyl-amino-azobenzene is used as the indicator) when a salmon pink color is reached. Titrating to a canary yellow color gives results a trifle too high but has been used as an end-point in this work as the difference is very small and the end-point much sharper than that encountered in titrating to salmon pink. Michaelis has further shown that beyond pH 3.0 the hydrogen ion concentration in N/10 HCl drops almost perpendicularly to pH 10. A change in this titration curve is due to the presence of acids other than free hydrochloric.

In the tables there are a few cases with a pH beyond 3.0 in which values from 2 to 10 are given under free hydrochloric acid. This is due to the fact that pH 4.0 (canary yellow color) was taken as the end-point for free hydrochloric acid titration.

The twenty-five cases of Group I secreted a fasting juice in which free hydrochloric acid varied from a small amount up to 94 meq. Following stimulation there was an increase of acid content in twenty cases; a few went up to 120 meq.

In Group II where HCl was secreted only after stimulation with histamine, the acid content occasionally rose to the high level of the first group; the general average was much lower. The relationship between the total chlorides and acid content of all groups is shown in figure 1.

In Group II there were ten specimens which had an hydrogen ion concentration between 3.4 and 5.0 as may be seen by referring to table II, Cases no. 10, 15, 16, 24, 25, 61, 64, 107, 118. The hydrogen ion concentration must be due to the presence of acids other than free HCl but at the present time it is impossible to do more than speculate on their nature.

The hydrogen ion concentration in the preponderant number of the achlorhydria cases was found to be about 7.0; if the pH was considerably greater, it is not to be accepted as quite correct since the escape of CO_2 will cause large errors.

In both of the groups secreting HCl there was a rise in acidity subsequent to the histamine stimulation and generally a decrease in the last, the 90 minute, specimen, and at times in the last two specimens. This observation has been made by numerous investigators and is mentioned here not as reiteration but because the interpretation of the diminution has been greatly discussed. A consideration of this point will be given later.

Bases

The change of secretion of total bases into the gastric juice presents an interesting series of phenomena. In Group I (patients who secreted HCl into all specimens) it was found that that amount of base varied inversely to the titratable acidity. In other words, during the period of secretion there was a drop in the milliequiva-

lents of total base per liter, and towards the end there was a rise in all cases except nos. 43, 54, 113, 116 and 118 where either the HCl or total chlorides did not fall. The amounts found in the fasting juice varied between 26 and 94 meq.; the general average of total base was 67. After stimulation the average dropped to 53 meq. and ranged between 30 and 84.

In Group II, those patients who secreted no free hydrochloric acid in the fasting juice but did after stimulation, the same phenomena were observed, only more intensified as there was often a very marked drop after stimulation. The total bases in the fasting juice varied between 60 and 120 meq., a general average of 97. After stimulation there was a marked drop to limits between 44 and 90 meq. with an average of 66 meq.

In the achlorhydrias, Group III, there was much less change in total fixed base after histamine stimulation; the curve of secretion being almost a duplicate of that of the chlorides of the same group. Figure 3 gives a clear-cut illustration of the changes in the three groups and may be superimposed on figure 1. The total variation in total fixed base in all four periods for the 44 cases was from 34 to 132 meq. The general average for each period was as follows: Control 88 meq.; 30 minutes, 88 meq.; 60 minutes, 89 meq.; 90 minutes, 95 meq.

It is important to note that some cases contained about the same number of milliequivalents of base throughout the periods of collection; i.e., if the fasting juice contained only 50 meq. the specimens collected after histamine also contained about the same number in contrast to the marked changes noted in Groups I and II. Likewise, if the fasting juice contained 100 meq. or more the following specimens contained 100 meq. more or less. There was an equal number of cases, however, who showed the ability to change secretion strength of bases. As was noted above, the same change occurred in the secretion strength of chlorides.

A very fair estimate of the changes in bases, which have been observed in the subdivisions of achlorhydrias, may be obtained by a reexamination of figure 2, since the figures for base agree more or less with those for the chlorides, although in individual instances it was seen that the total bases were several milliequivalents per liter higher than the corresponding amounts of chlorides per specimen. This very important inequality will be discussed further on.

Ortho-phosphates (Inorganic)

The estimation of inorganic phosphorus would seem to be of some importance since it is usually found in greater concentration than in the blood, except during periods of large volume output and relatively high acidity.

In Group I the limits of inorganic phosphate lie between 0.5 and 3.2 meq. of phosphate ion in the resting juice. After histamine there was generally a decrease in the concentration and in cases with high volume output the level decreased, at times, to 0.3 meq.

In Group II the limits of the phosphate in the acid free resting juice lie between 1.1 and 5.4 meq., a substantially higher level than that noted for the resting juice of the preceding

group. After stimulation there is usually a decrease in amount but as the volume and acidity of this group seldom reach the heights of Group I, it is rare to find a decrease equal to the limits of Group I.

In Group III (achlorhydrias) the limits of the phosphate in the fasting specimen lie between 1.1 and 5.6. As with the chlorides and bases there is much less variation in the amount of phosphate of this group than in Groups I and II. The level remained more or less constant throughout the period of observation. This is illustrated in chart 1.

Carbon Dioxide

In cases where the CO_2 content was estimated the gastric juice was collected under a thick covering of oil. It is recognized that the method allows of only an approximate determination but even so it has been possible to account for several apparent inaccuracies in the acid-base ratio. The CO_2 content as determined represents minimum values.

A recheck of the amounts of CO_2 recovered in relation to the pH of the juice, permits the opinion that, within fairly rough limits, the results are of value. The high CO_2 values were always found with cases having a pH beyond 7.0, and at times 8.0. This last figure can be obtained only by loss of CO_2 to the air, as has been said above.

In cases in which hydrochloric acid was present in all specimens, Group I, the CO_2 content was usually between 1 and 4 volumes per cent.

In the non-acid fasting specimens of Group II, there are unfortunately only five estimations. Those specimens analyzed, however, have a CO_2 content of from 10.0 to 14.5 volumes per cent. Some of these contained bile. After stimulation the CO_2 assumed the same value as in Group I.

The estimations made on Group III, the achlorhydrias, showed a general upward trend of CO_2 content, varying from 5.5 to 67.0 volumes per cent. In a rough way the CO_2 content was proportional to the pH and had no direct relationship to bile or trypsin content.

Trypsin

The measurement of trypsin represents the milligrams of non-protein nitrogen produced from 2.0 c.c. of 0.5 per cent casein in phosphate buffer of pH 7.5 by the action of 1 c.c. of a 1:10 dilution of gastric juice incubated for half an hour at 37.5° C.

In Group I amounts varying from none to 4.0 mg. have been found. The few cases showing a biliary regurgitation have usually been found to have higher values but at times trypsin has been demonstrated in the absence of bile. There may be a bile tinge to the gastric juice without any demonstrable trypsin.

In Group II there was a marked increase in the amount of trypsin found in the acid free resting juice either with or without the presence of bile. The largest amount found was 11.0 mg. After histamine stimulation occasionally larger amounts were found than in the comparable specimens of Group I and occasionally trypsin disappeared with the secretion of gastric juice.

The achlorhydrias as a group have much the greater content of trypsin, in fact amounts up to 18.0 mg. were not uncommon. It was not entirely absent in any specimen but Case number

70 had very small amounts, and strangely enough this patient regurgitated bile.

Discussion

It is possible to correlate some of the data at hand and to give some interpretations.

In the acid secreting cases a high volume of secretion was always associated with a high content of chloride and hydrochloric acid.

As noted under volume the typical case runs its highest secretion during the early periods after stimulation and gradually decreases as the stimulation ceases. From figure 1 it has been possible to show that the same type of curve is also found in the chloride and the acid content of the successive periods. However, the volume, the total chloride and the acid content vary considerably from case to case; and some cases with small volume secretion will have a high chloride and acid content—this occurred in one case secreting a high mucus-like fluid.

In chart 2 the relation of volume to total chlorides has been plotted. The achlorhydrias, it is here shown, secrete the chlorides at a lower level and associated with this there is generally a low volume.

In chart 3 the relation of volume to acid content has been plotted. In order to be able to include the achlorhydrias, the free hydrochloric plus the so-called combined or total acidity was used. The value of the latter averaged about 10 meq. The same points as in chart 2 are illustrated; i.e., when there is a large volume of secretion, the acid content is high, but here there are some very noticeable exceptions in which a high acid content is associated with a very low volume.

In the specimens without free hydrochloric acid the volume is seen to fall generally below 40 c.c. and, in the large percentage, below 20 c.c. per thirty minute period. The estimation of the combined or total acids, i.e., those substances, acid or buffer, which hold the gastric juice below pH 3.0, has a certain value but it would be erroneous to consider the value as having the same relation to volume as has the estimation of hydrochloric acid.

Influence of Duodenal Regurgitation

It may be interesting to consider the data in regard to the influence of duodenal regurgitation on the regulation of the acidity. Figures 1 and 3, which have been presented to show the relationship between the various electrolytes, demonstrate the fact that in the acid secreting cases there is a normal rise and fall in the acid curve and that furthermore there is a smaller but yet, none the less, definite rise and fall in the secretion of chlorides. In accord with the theory of duodenal regurgitation, the fall in acid should be accomplished by regurgitated alkaline duodenal contents.

In order to throw further light on the subject, specimens were examined for the presence of bile and of trypsin. These were noted to appear in a most irregular manner throughout the different periods of extraction. At times one or both of them were found when there was a diminution of acidity in the fourth specimen but as frequently they were not present. They were found not only when there was no decrease in the amount of acid but also when there was no increase in the

amount of the chlorides, making it even more unlikely that regurgitation would explain the changes of acidity.

It is certainly possible for the duodenal contents to diminish the amount of gastric acidity during the periods of collection or duration of normal digestion. This action is of secondary importance, however, as it has been shown that the fall in acidity takes place without its aid and that the amount and strength of hydrochloric acid decreased with the cessation of stimulation.

Amount of Electrolytes Secreted

Figure 4, for ease in comparison, presents the typical secretion of electrolytes of each of the three groups, and of a normal blood serum. The latter represents the findings in one of the cases in Group I, on whom serial blood and urine analyses were made at the time when the fasting specimen of gastric juice was taken. The value for protein is represented by the amount of base fixed by serum albumen and serum globulin at pH 7.35. The albumen-globulin ratio was taken as 1.8. Calculations were made by the formula of Van Slyke et al.[16]:

$$\text{B protein} = 0.243 \text{ protein}$$

The difference between the amount of base and the cation was considered to be due to organic acids.

Rôle of Bases and Bicarbonates

The secretion of base into the gastric juice is interesting. In those cases which have the ability to secrete hydrochloric acid there is a post-stimulation drop in the content of the base which is in inverse proportion to the increase in the content of acid. In these cases it has been shown that except for an occasional slight difference (usually within the limit of experimental error) there is a mathematical equality between the determined cations (hydrogen and bases) and the anions (chloride and phosphate). In this relation the phosphate is usually so low that its presence may be disregarded. This agreement is shown clearly in figure 4, which illustrates the relation between base and hydrochloric or free acid with the changes in the chlorides.

The course of a typical case is demonstrated in figure 5. The fasting contents contained 10 meq. of hydrogen ion (free HCl) and 75 meq. of bases; this was almost exactly counterbalanced by the 83 meq. of chloride. During the various phases of secretion this relationship between the anion and cation remained about the same although there was a decided increase in the milliequivalents secreted under the stimulation of histamine.

The relationship between the bases and chlorides in the group of achlorhydrias is shown in graph 5. It is demonstrated that although many of the amounts in the individual specimens are in close accord, there are others, rather numerous, which fall outside the limit of experimental error. This difference is found not only in cases of true achlorhydria but also in the acid-free resting juice of patients who secreted hydrochloric acid after histamine stimulation. See Cases no. 88, 95, 102, 112, etc.

In Case no. 95 which secreted acid after histamine stimulation the relationship between the anions and the cations of the acid-containing specimens was almost equal as is seen in figure 6. In the fasting juice of pH

7.0 the bases were greater than the chlorides by 15 meq. The carbon dioxide content of the specimen was 11 meq., and of the acid-containing specimens about 3 volumes per cent, too small an amount to be of significance.

A consideration of the achlorhydrias shows that the content of CO_2 plays an important rôle in equalizing the base and acid columns. Case no. 112 has been selected from a series of similar cases to illustrate this point in figure 7. There are, however, cases of achlorhydria from which but small amounts of CO_2 have been recovered. These are generally cases whose gastric juice has a pH below 7.0.

It is known that the CO_2 content of hepatic duct bile and pancreatic fluid is high and consequently it seems only reasonable that the regurgitation of these fluids into a nearly neutral gastric juice would result in the presence of CO_2. In this series several of the specimens on which CO_2 determinations were made showed no evidence of bile and also the trypsin estimations were not unusually high. Consequently it seems quite definite that CO_2 is present in the achlorhydric gastric juice of human beings.

The Comparison of Total Chlorides of Gastric Juice and Blood Plasma

The amount of chlorides of the gastric juice in one case reached 158 meq., a considerably higher figure than that of the blood serum, although the sum of the blood serum bases is about equal to it. In the majority of cases the amount was much lower, making a general average for 46 cases of 120 meq. of gastric juice chlorides. Therefore, although the milliequivalents per liter of chlorides secreted were lower than the total number of anion or cation milliequivalents per liter of the blood, the chlorides of the gastric juice of the cases of Group I are almost always higher than those of the blood serum.

The acid free resting juice of patients who have the ability to secrete hydrochloric acid after histamine had an average of 91 meq. of chloride, varying between the limits of 58 and 113. This may be compared with fasting and secretion juice of the true achlorhydrias in which there was a general average of 83 meq., varying between 37 and 115. In both of these groups the chloride level was always lower than the total milliequivalents per liter level of bases in the serum but sometimes was above and sometimes below the level of the serum chlorides.

The Secretion Concentration of Bases and Free Hydrochloric Acid

The point cited above naturally led to the question of the secretion concentration of the salts and acid found in the extracted gastric contents. The term *secretion concentration* is used to represent the concentration at which the salts and free hydrochloric acid are produced by the cells before dilution. The easier method of approach would seem to be by determination of the secretion concentration of salts in cases of achlorhydria and in the acid free resting juice of Group II:

a. To see if there was a marked difference in secretion concentration from case to case.
b. To determine the changes, if any, which took place at various periods of analysis in the cases of achlorhydria.

As a solution to the first problem

several cases have been collected into table V. The sixth column shows that in the acid free resting juice and in corresponding achlorhydria specimens there is a marked variation in the base content from case to case. When the total content, as determined, was reckoned as the equivalent quantity of sodium chloride (NaCl), the salt content so calculated approximated the actual salt content of the juice but did not include the Na_2HPO_4 and NaH_2PO_4. Since there are no complicating factors such as a change in the chemical constituents of fluid, the concentration of salts in the extracted material represents their secretion concentration into the gastric juice. Furthermore, it must be kept in mind that this fluid is a different fluid from that which appears with the acid secretion in which there is a change in the chemical constituents. Consequently within the limits set in the above argument there is considerable variation in the secretion concentration of salts into the unstimulated acid-free, and the achlorhydria, stomachs.

The secretion concentrations in the former group varied from 333 to 650 mg. per cent. In the stimulated and unstimulated gastric juice of the achlorhydrias, the variation was even more pronounced, namely from 225 to 794 mg. per cent.

The solution of the second problem, as far as the cases of achlorhydria are concerned, is equally simple and the results may likewise be seen in table V. There was always some, and frequently much, change. In one of the cases of pernicious anemia, an initial fasting secretion concentration of 232 mg. per cent was increased to 632 mg. per cent after histamine stimulation. Case no. 44 is of some interest because hydrochloric acid appeared only in the 60 minute specimen. The salt concentration in the fasting juice was 510 mg. per cent, changing to 435 mg. per cent in the specimen collected for 30 minutes after stimulation.

Another group of these cases, however, showed but little variation in secretion concentration from specimen to specimen. It has been impossible to make any satisfactory classification for diagnosis on the basis of stationary or changing levels of secretion concentration after stimulation.

The determination of the secretion concentration of the salts in the acid secreting cases is not simple because the question of the influence of other molecules such as HCl in varying quantities is to be considered. This in turn brings up several points about the secretion of the hydrochloric acid which would be interesting to solve:

a. Is it secreted at different concentrations in different individuals?
b. Is it secreted at different concentrations at various phases of secretion in the same individual?
c. When the secretion of hydrochloric acid takes place does the stomach secrete salts at the prestimulation level or does it secrete them at higher or lower levels?

Before these questions can be answered, a few ideas must be explained.

With the production of acid, there is always an increase in the content of chlorides but this increase is insufficient in amount to account for all the hydrochloric acid. This inequality is compensated for by a drop in the amount of base, as has been seen in figures 1 and 3. This decrease may

have nothing to do with the secretion of base and be only a result of dilution by hydrochloric acid in the presence of an increasing or decreasing salt secretion, either in respect to amount or to concentration.

As an essential point in this theory of secretion it is necessary to admit of two types of cells: one group secreting hydrochloric acid in pure solution; the other secreting the various bases as salts (chiefly as chlorides). The anatomical arrangements of the organ and its physiology makes it rather difficult to promulgate another belief. This is especially true in consideration of the secretion concentration of salts in the cases of achlorhydria.

The method for the determination of the secretion concentration is as follows: In Case no. 98, there were 45 c.c. of gastric juice extracted as fasting secretion. This contained of base, 85 milliequivalents per liter; acid, 10 milliequivalents per liter; phosphate, 0.8 milliequivalent per liter; and total chloride, 75 milliequivalents per liter. Due to its small amount, phosphate may be left out of the reckoning. Base has been calculated as NaCl with a molecular weight of 58, and therefore a milliequivalent or 1 c.c. contains 0.058 gms. NaCl. The molecular weight of HCl has been calculated as 36 and a milliequivalent as containing 0.036 grams HCl.

The amount of free HCl in 45 c.c.
10 milliequivalents per liter $= .01$ milliequivalents per c.c.
$.01 \times 45 = .45$ milliequivalents free HCl in 45 c.c.
$.45 \times .036 = .0162$ grams free HCl in 45 c.c.

But 10 meq. HCl + 75 meq. NaCl = 85 meq.
And HCl represents $\frac{10}{85} = .1176$ milliequivalents secreted.

Therefore $.1176 \times 45 = 5.29$ volume of secretion of pure HCl necessary to produce the quantity found in total volume of gastric juice.

And X, the grams HCl in 100 c.c. $5.29 : .0162 = 100 : X$
But $X = \frac{100 \times .0162}{5.29}$
$= .306$ grams

And therefore HCl as secreted by the acid producing cells before dilution
$= .306$ per cent

But since $.0162 = .45 \times .036$
and $.1176 = 10/85$
and $5.29 = .1176 \times 45$

Therefore X, the grams of HCl in 100 c.c. or the secretion concentration of HCl as secreted by the acid producing cells before dilution, is by interpolation as follows:

$$X = \frac{100 \times .0162}{45 \times .1176} = \frac{100}{45} \times \frac{.0162}{.1176}$$

$$= \frac{100}{45} \times \frac{45 \times .036 \times .01}{10/85}$$

$$= \frac{100}{45} \times \frac{45 \times .036 \times .01 \times 85}{10}$$

$= .10 \times .036 \times 85$
$= 0.10 \times .036 \times$ number of milliquivalents of total chlorides in the specimen.

The same formula may be used in estimating the secretion concentration of sodium chloride by substituting .058 for .036.

It has already been shown that in the cases of achlorhydria and in the acid free resting juice of patients who secrete free hydrochloric after histamine the secretion concentration of sodium chlorides (bases calculated as NaCl) is subject to wide variation, not only from patient to patient, but in successive samples taken before and after histamine stimulation in the same patient. By the use of the formula just explained, it has been possible to bring to light several interesting observations on acid containing specimens.

(1) Hydrochloric acid was secreted at varying concentrations between the limits of 316 to 564 mg. per cent. This applied to all the specimens from the 46 acid secreting patients of Group I and Group II.

During the period of observation on the average patient (before and after histamine stimulation) there was a change in the secretion concentration of hydrochloric acid. It was lowest in the fasting specimen and rose to its highest level during the height of stimulation, usually to fall somewhat towards the end of stimulation. With the diminution of secretion concentration there was also a decrease in volume of free hydrochloric acid. In other words the concentration of the pure hydrochloric acid solution as secreted followed a curve similar to that of the secretion of the determined total chlorides as in figure 1.

(2) Sodium chloride was secreted at varying concentrations between the limits of 510 and 916 mg. per cent. This also applied to all the specimens of Groups I and II.

That which was true of the variation of secretion concentration of free hydrochloric acid in individual cases, is true also of sodium chloride. The lowest secretion concentration was generally found in the resting specimen and the highest during the height of stimulation to fall off slightly towards the end of secretion. In one important manner there was a lack of parallelism to the free hydrochloric acid secretion concentration: towards the end of stimulation there was a fall in the volume of hydrochloric acid secreted. This was not so markedly reflected in the salts since usually the post-stimulation volume of secretion of salt solution remained at the same content for some time. The secretion concentration of base calculated as NaCl varied directly as the secretion of the determined chlorides. This is as true of the achlorhydrias as of the acid secreting cases.

The increase in the percentage concentration of hydrochloric acid in the extracted material is, therefore, due to two factors (a) the increased volume output of hydrochloric acid produced by the stimulation of the acid secreting cells and (b) to the increased con-

centration of the acid produced by the cells at the height of stimulation.

The diminution found in the concentration of salts in the successively extracted acid containing specimens is also due to two factors: (a) Although the volume of salt solution secreted may be somewhat increased, the volume secreted is relatively small in comparison to the volume of acid solution secreted. The figures for this statement are included in table V. (b) If the salt secretion strength had continued at the prestimulation level the concentration in the extracted materials would have been still lower as is seen in table V; therefore, its ultimate content could only have been produced by increase in secretion strength.

Conclusions

Neutral salts, phosphates, and CO_2 are normally secreted into the resting stomach. There is no constant strength at which the CO_2 and the salts are secreted as they vary markedly in different patients. Hydrochloric acid may or may not be found in the resting juice; its presence probably represents a different physiologic process than that represented by the resting state.

Histamine provokes an increased secretion of gastric juice into most stomachs. It is probably normally accompanied by the secretion of hydrochloric acid. A large volume of secretion was always accompanied by free acid. It seems that acid is secreted throughout the duration of the stimulation and that as the stimulus wears off the production of acid ceases, and the secretion returns to its resting state. The volume of secretion tends to run a course parallel to the acid. Variations, which may be pathologic, have been noted from this statement and qualifications have been listed above. As the amount of acid increases there is an increase in the secretion concentration; this is also true within the restrictions noted above.

The secretion of the neutral salts continues during the period of stimulation and increases in secretion concentration parallel with the acid. On the other hand the volume output is considerably less than that of hydrochloric acid and a diminishing percentage content of the neutral salts is found in the extracted material in contrast to the increasing percentage of hydrochloric acid. As the stimulus to secretion wears off the production of hydrochloric acid ceases. The volume of salt solution secreted by the cells also diminishes but evidently the concentration of the salt solution continues at a more elevated level for a varying period of time.

Phosphates diminish in concentration in the extracted juice during the successive half-hour periods of observation.

CO_2 is not found in the juice containing free hydrochloric acid but appears in amounts related to the pH of the achlorhydria juice.

The gastric mucosa of many achlorhydrias still retains the ability to secrete salts at various concentrations although for some unknown reason the ability to secrete hydrochloric acid is lost.

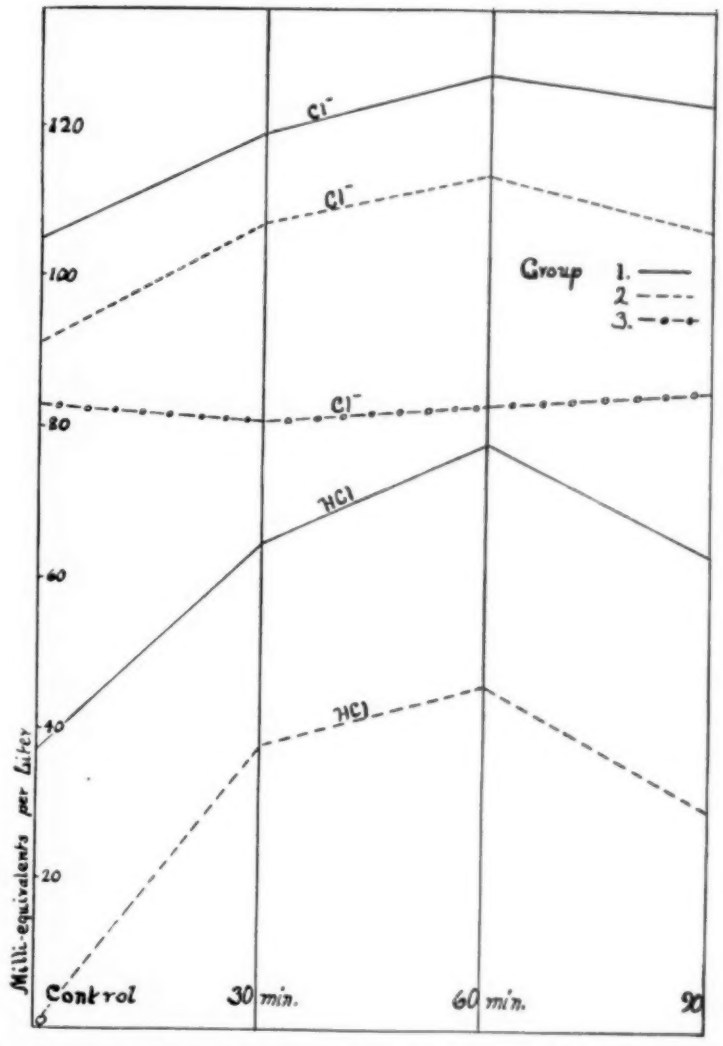


FIG. 1. Composite chart of total chlorides and free hydrochloric acid in Groups I, II and III. Variations before and after histamine stimulation as averaged from 20 or more cases per group.

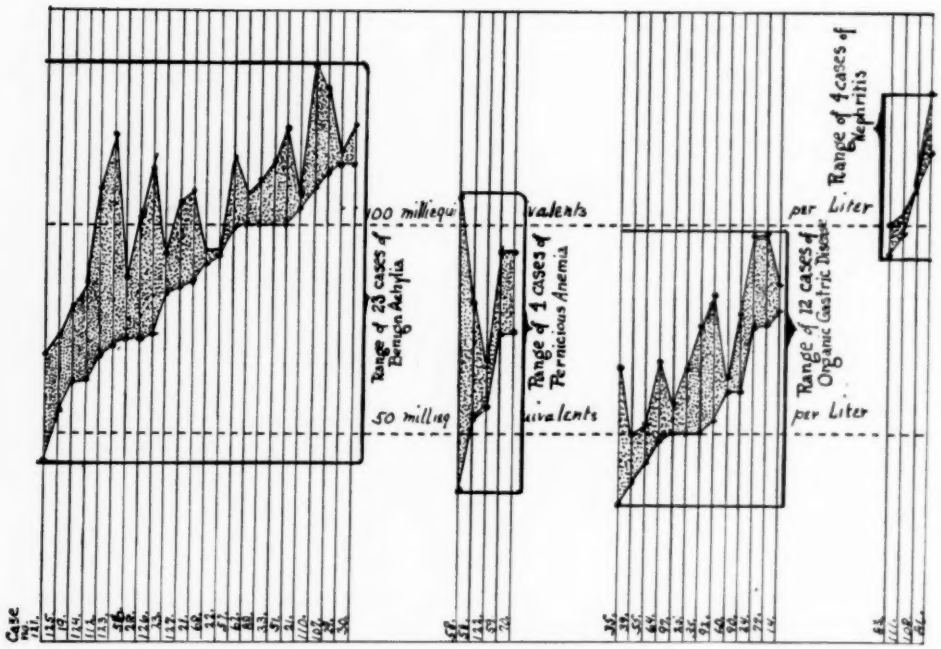


FIG. 2. Range before and after histamine stimulation of total chlorides per case of achlorhydria, grouped according to diagnosis.

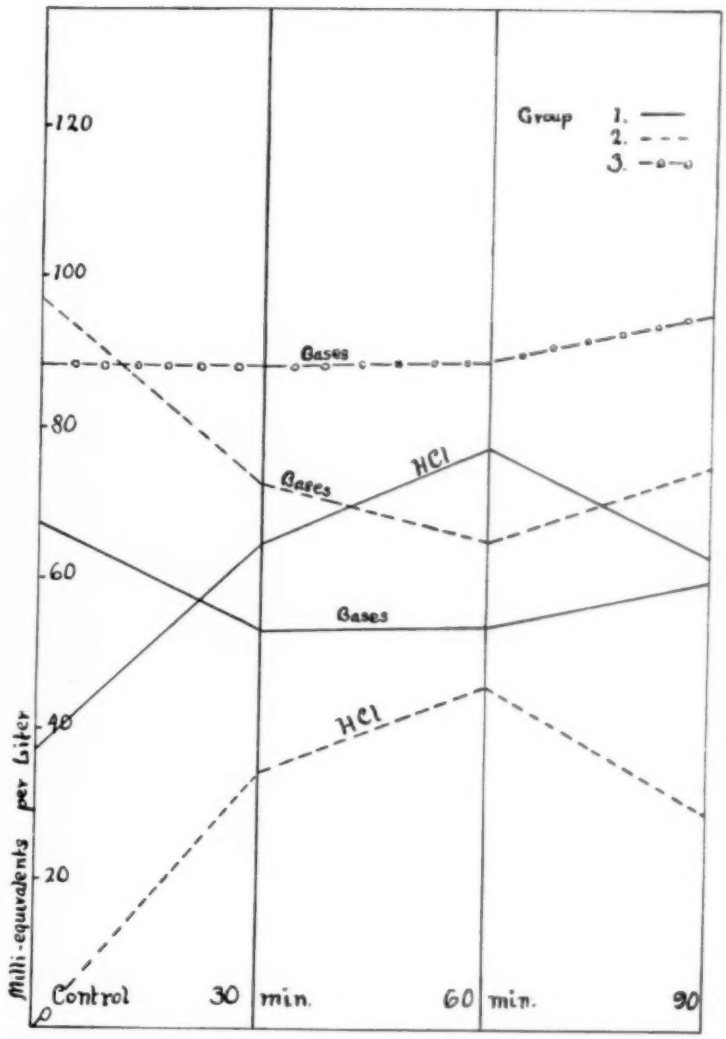


FIG. 3. Composite chart of bases and free hydrochloric acid in Groups I, II and III. Variations before and after histamine stimulation, averaged from 20 or more cases per group.

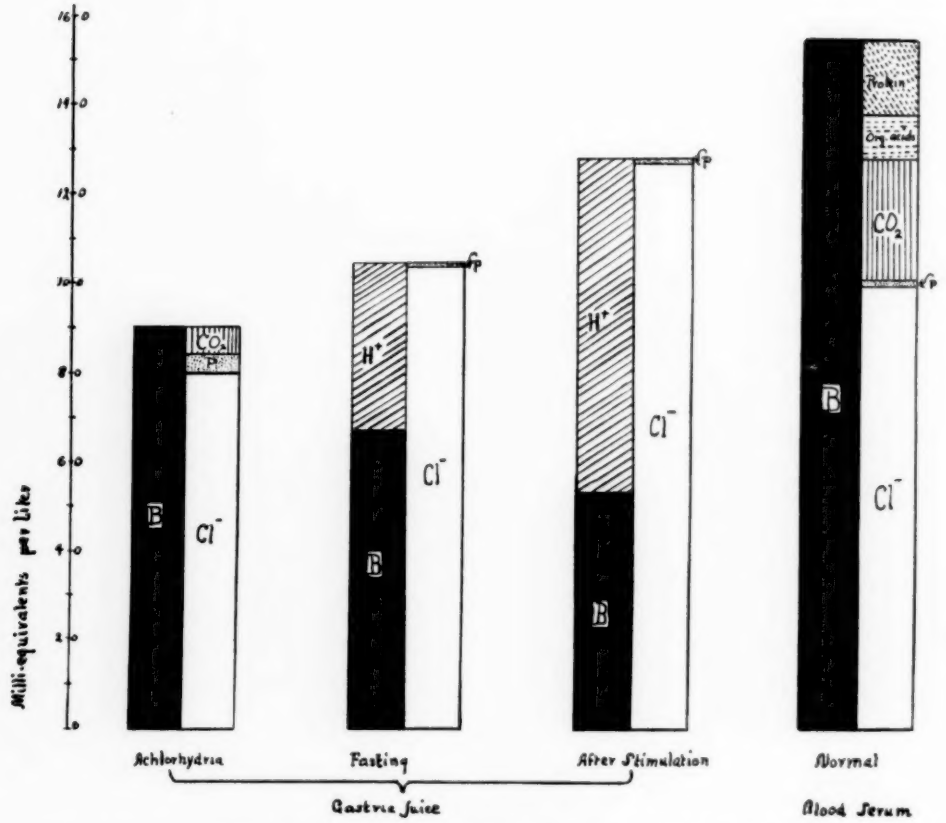


FIG. 4. Comparison of the total electrolytic content of typical specimens of gastric juice with the electrolytic content of normal blood serum.

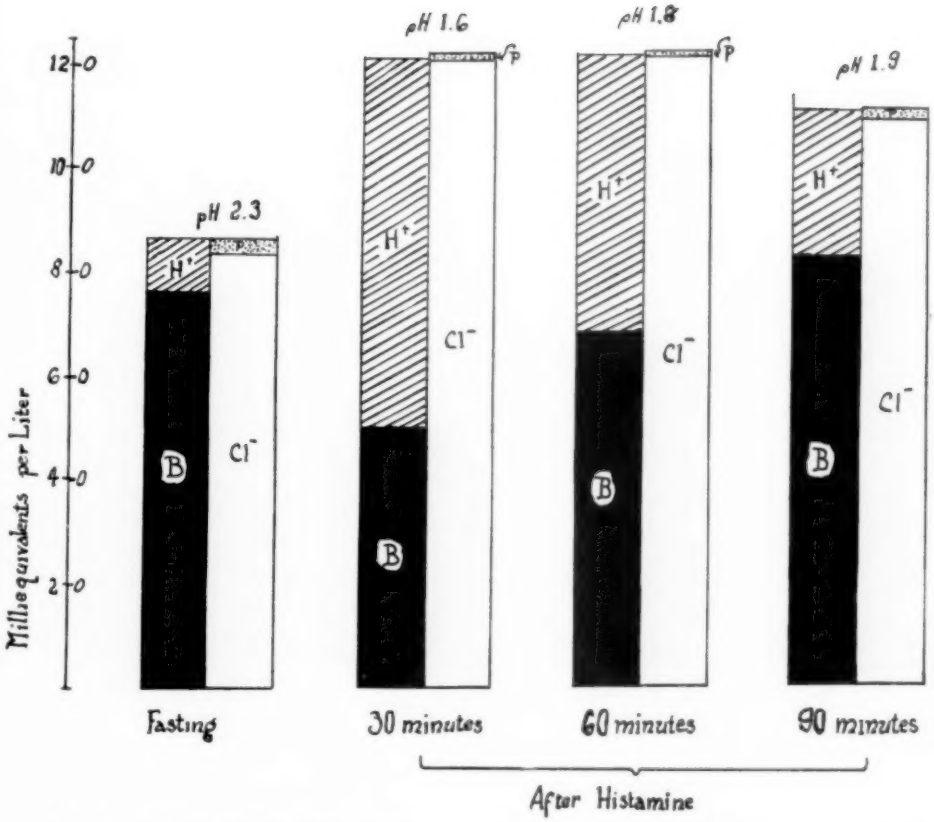


FIG. 5. Typical normal case of Group I showing electrolytic changes during histamine stimulation.

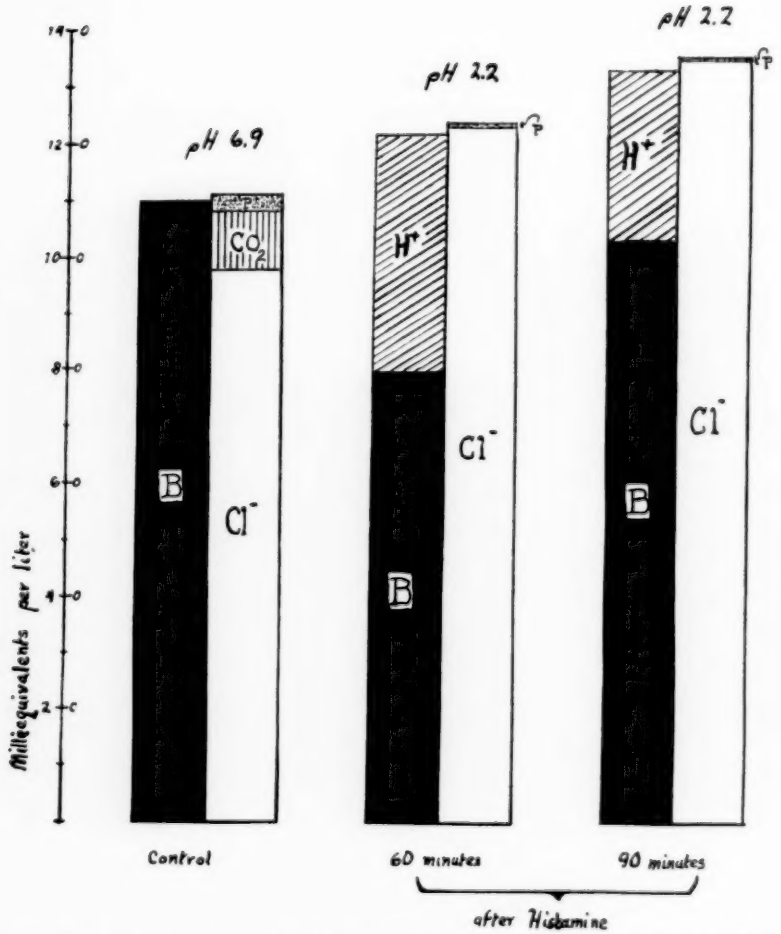


FIG. 6. Typical normal case in Group II showing electrolytic changes during histamine stimulation.

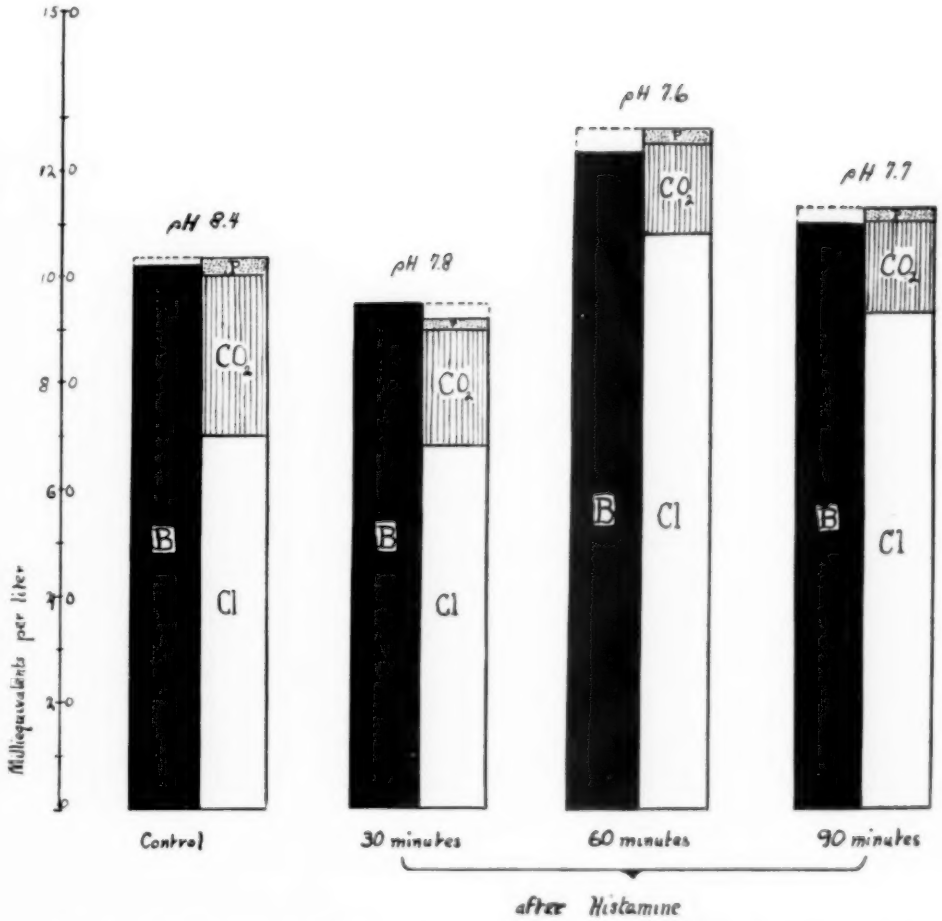


FIG. 7. Typical case in Group III (achlorhydria) showing electrolytic changes during histamine stimulation.

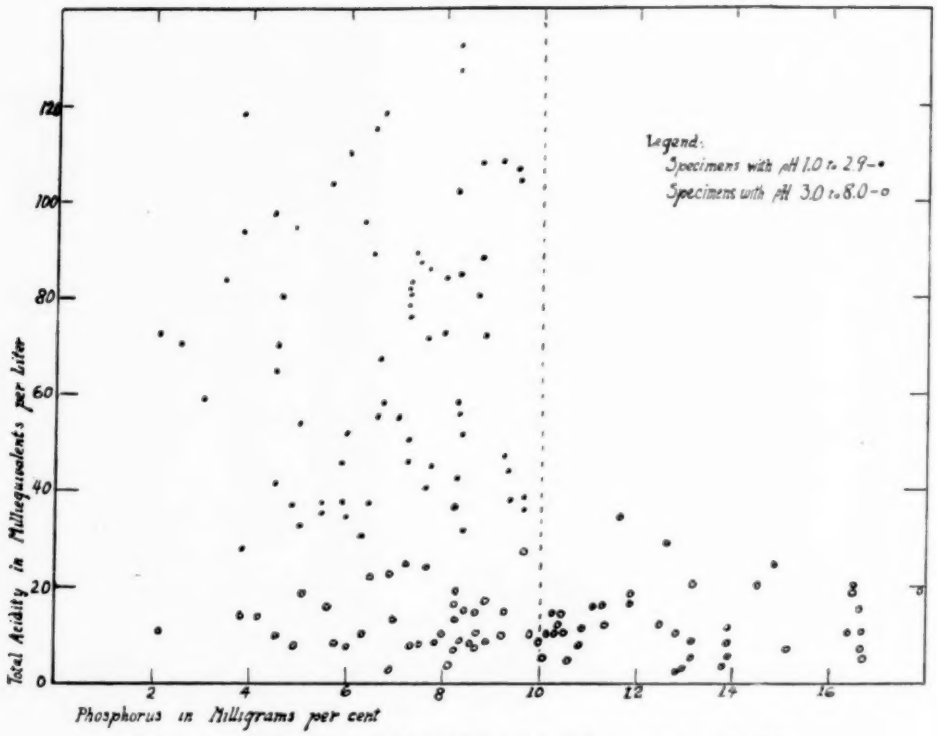


CHART 1. Relation of total acidity to phosphorus in gastric juice.

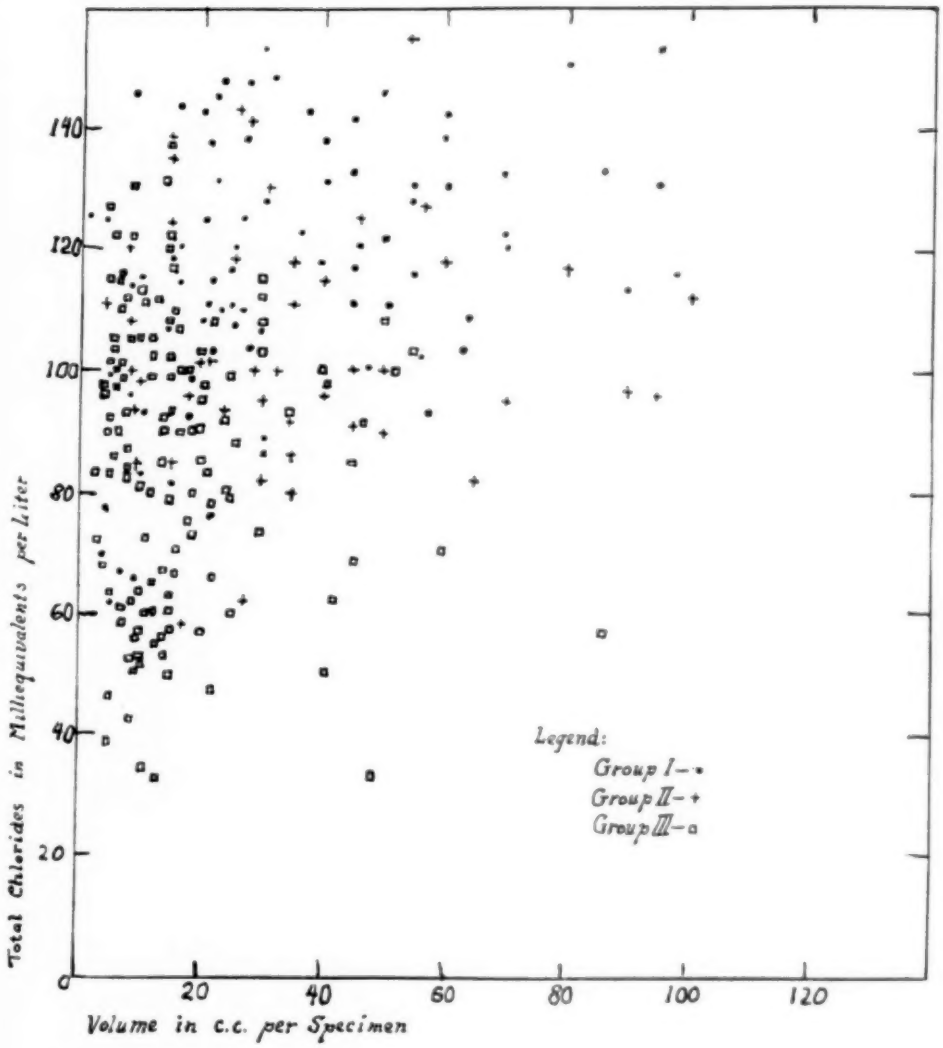


CHART 2. Relation of total chlorides to volume of extracted gastric juice in the several groups.

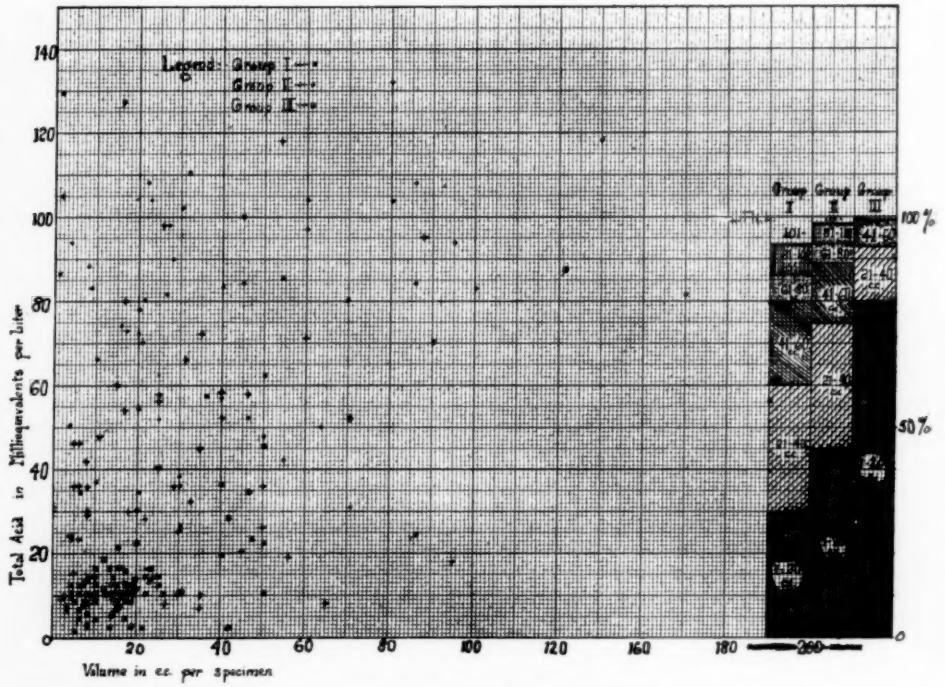


CHART 3. The dots, crosses and squares represent the relation of total acidity to the volume of the extracted specimen of gastric juice in fifty cases. The block figures represent the percentage of specimens for each group arranged according to the volume content. The entire 102 cases were used in the estimation.

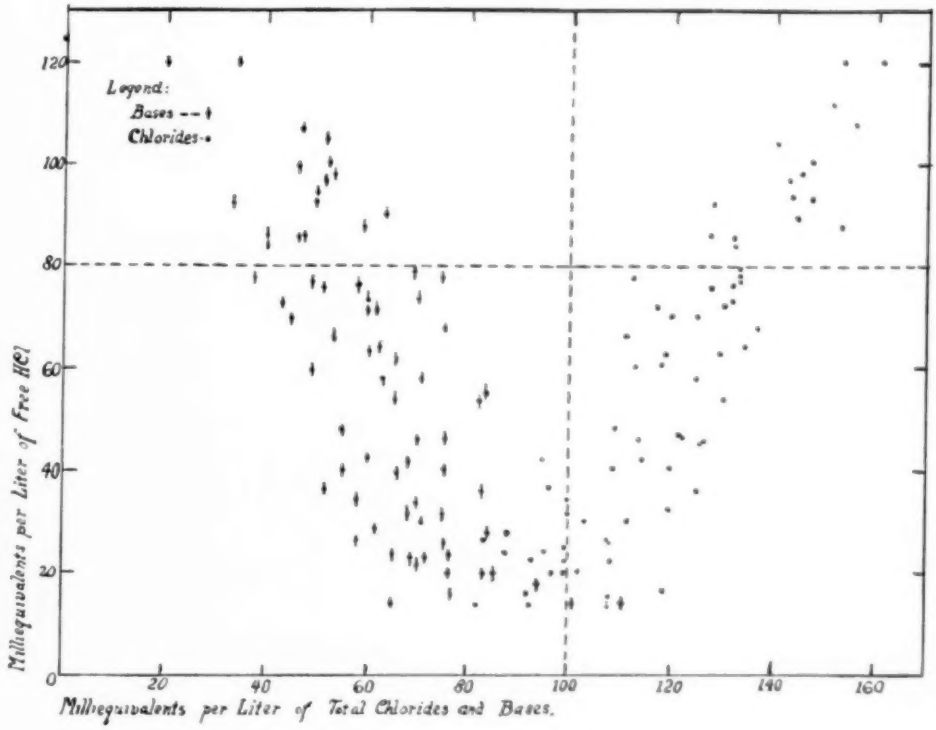


CHART 4. Relation of free hydrochloric acid to bases and total chlorides.

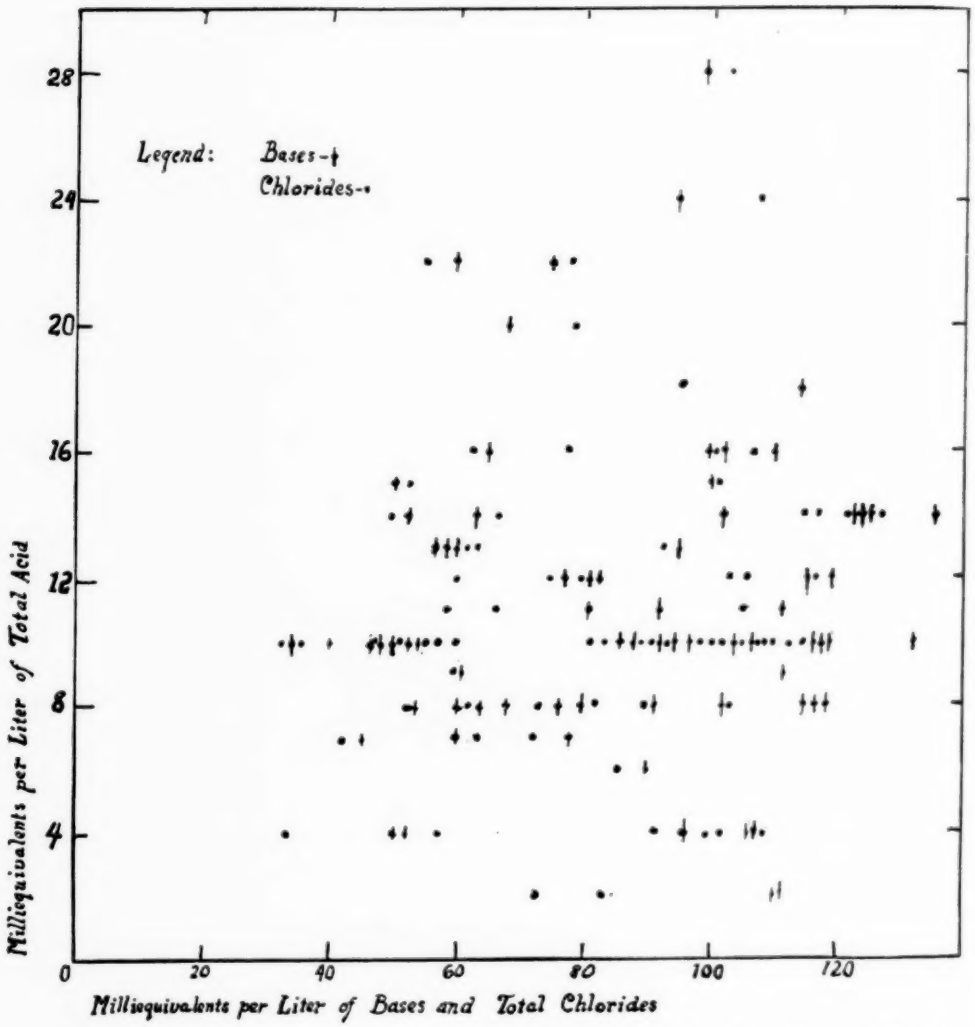


CHART 5. Relation of total acid to bases and total chlorides in specimens with pH 3.0 to 8.0.

TABLE I
Data on Patients in Group I Who Secrete Free Hydrochloric Acid into All Specimens of Gastric Juice

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME c.c.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
6.	F.*	Clear	1.6	15	21	117	94	2.7	..	..	..
	30	Clear	1.4	74	77	133	59	2.4	..	..	..
	60	Clear	1.2	50	97	145	51	3.0	..	..	..
	90	Clear	1.4	22	64	131	62	2.6	..	..	..
7.	F.	Clear	1.8	10	23	93	69	3.0	..	..	..
	30	Clear	1.6	64	40	108	66	2.3	..	..	..
	60	Clear	1.5	20	66	114	54	2.3	..	..	..
8.	F.	Clear	1.6	10	54	81	26	2.1	..	..	..
	30	Bile tr.	1.4	80	94	120	30	1.5	..	..	..
	60	Clear	1.6	22	20	108	84	1.1	..	..	..
8.	F.	Clear, mucus.	1.6	30	24	88	65	2.7	..	2.1	..
	30	Clear, mucus.	1.4	100	74	120	45	1.8	..	2.1	..
	60	Clear, mucus.	1.2	95	85	130	40	1.2	..	4.0	..
	90	Clear, mucus	1.2	55	86	130	40	1.5	..	2.1	..
13.	F.	Clear	..	20	20	97	76	3.2	..	..	..
	30	Clear	..	90	60	113	50	3.2	..	..	..
	60	Clear	..	30	92	128	33	2.6	..	..	..
	90	Clear	..	8	78	113	38	2.7	..	..	..
31.	F.	Clear	1.9	190	46	113	70	2.7	..	..	0
	30	Clear	1.2	150	112	151	46	2.1	..	..	2.0
	60	Clear	1.2	32	100	148	52	1.9	..	..	4.3
	90	Clear	1.2	27	90	147	62	1.8	..	..	3.0
38.	F.	Mucus	..	4	46	77	36	..	..	..	..
	30	Mucus	..	6	23	67	43	..	..	..	..
	60	Mucus	..	4	12	68	56	..	..	..	..
42.	F.	Clear	2.3	46	42	120	75	2.7	..	..	tr.
	30	Clear	1.7	40	73	117	43	2.6	..	..	1.0
	60	Clear	1.8	45	75	132	58	2.7	..	..	1.5
43.	F.	Clear	2.1	20	62	124	65	2.8	..	2.1	0
	30	Clear	1.9	27	74	138	69	2.3	..	2.1	0
	60	Clear	1.3	80	120	150	34	2.7	..	2.1	0
	90	Clear	1.3	16	120	143	20	2.7	..	4.0	0
45.	F.	Bile tr.	2.5	..	32	118	78	2.4	..	3.0	0.
	30	Clear	2.2	170	72	130	60	2.4	..	4.0	0.
	60	Clear	2.2	345	72	131	60	2.4	..	3.0	0.
	90	Bile tr.	2.1	55	76	127	50	2.4	..	4.9	0.
54.	F.	Mucus	1.7	1	78	125	47	..	..	..	tr.
	30	Mucus +++	1.5	2	98	140	44	..	..	..	tr.
	60	Mucus ++	1.4	2	121	158	40	..	..	..	tr.
	90	Mucus	1.5	4	89	125	35	..	..	..	0

*F.--Fasting or control specimen.

TABLE I (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME c.c.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
65.	F.	Clear	1.6	20	94	143	50	3.1	..	..	0
	30	Clear	1.6	23	93	147	50	3.1	..	..	0
	60	Clear	1.7	22	98	145	53	2.8	..	..	0
	90	Clear	1.8	21	68	137	75	2.7	..	..	0
79.	F.	Clear	2.4	55	30	103	75	1.4	..	..	0
	30	Clear	1.7	86	73	132	60	1.1	..	..	0
	60	Bile "B"	2.0	36	46	122	75	1.0	..	..	0
	90	Bile "A"	2.3	40	24	96	75	1.6	..	..	0
94.	F.	Clear	2.4	8	20	95	73	2.0	..	2.1	0
	30	Clear	1.9	21	58	102	48	2.0	..	2.0	0
	60	Clear	1.5	16	62	120	62	1.0	..	1.9	0
	90	Clear	1.8	9	72	145	70	0.4	..	1.9	0
98.	F.	Clear	2.8	45	10	85	75	1.7	..	2.6	2.0
	30	Clear	1.6	70	70	121	50	0.8	..	1.7	0
	60	Clear	1.8	50	52	121	68	0.5	..	1.8	1.0
	90	Clear	1.9	30	28	108	82	1.1	..	2.1	0
99.	F.	Clear	2.1	25	42	108	50	0.5	..	8.8	tr.
	30	Clear	1.8	60	82	138	48	0.8	..	1.7	tr.
	60	Clear	1.6	60	94	141	48	0.6	..	1.7	tr.
	90	Clear	1.6	45	92	141	54	0.4	..	1.2	tr.
101.	F.	Clear	2.8	30	12	88	82	1.0	..	2.1	0
	30	Clear	1.9	50	36	110	84	0.6	..	2.1	0
	60	Clear	1.8	25	78	118	78	0.3	..	3.0	0
	90	Clear	1.7	40	50	131	84	0.3	..	2.1	0
104.	F.	Bile tr.	2.3	18	19	92	82	1.6	..	4.9	2.4
	30	Clear	1.5	22	76	131	60	0.8	..	2.1	0
	60	Clear	1.2	130	108	143	42	0.7	..	1.7	0
	90	Bile tr.	1.9	25	50	110	70	1.0	..	1.7	3.0
113.	F.	Clear	2.6	63	8	103	92	1.4	..	..	..
	30	Clear	2.4	47	26	100	76	1.0	..	..	..
	60	Clear	2.3	130	58	111	53	1.0	..	..	..
	90	Clear	2.3	90	48	105	51	1.0	..	..	..
114.	F.	Clear	..	29	42	103	68	..	..	..	..
	30	Clear	..	5	12	62	50	..	..	..	..
	60	Clear	..	8	15	65	50	..	..	..	..
	90	Mucus ++++	..	13	0	78	78	..	..	..	..
114.	F.	Light green	..	45	27	99	68	1.4	..	..	..
	30	Clear	..	15	20	81	48	1.5	..	..	..
	60	Clear	..	45	68	112	37	1.0	..	..	..
	90	Light yellow	..	25	43	110	67	1.9	..	..	..

TABLE I (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME C.C.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
115.	F.	Clear, green.	2.6	57	28	93	59	..	..	..	..
	30	Clear, green.	2.2	28	40	110	71	..	..	..	..
	60	Clear, green.	1.9	60	76	130	56	..	..	..	..
	90	Clear, green.	2.0	27	70	125	56	..	..	..	..
116.	F.	Clear	..	18	36	97	58	1.9	..	..	..
	90	Clear	..	98	73	116	39	1.4	..	..	..
	60	Clear	..	45	80	116	37	1.4	..	..	..
	90	Clear	..	55	73	116	39	1.4	..	..	..
117.	F.	Bile tr.	2.4	10	40	115	68	2.4	..	..	0
	30	Bile tr.	2.6	15	30	107	75	2.0	..	..	0
	60	Bile tr.	2.6	21	34	111	67	2.0	..	..	0
	90	Bile tr.	2.4	12	36	113	69	2.2	..	..	0
118.	F.	Clear	1.6	40	86	138	50	1.9	..	..	..
	30	Clear	1.4	38	100	142	44	1.5	..	..	..
	60	Clear	1.4	30	116	152	39	1.7	..	..	..
	90	Clear	1.3	95	118	153	35	1.7	..	..	..

TABLE II

Data on Patients in Group II Who Secrete no Free Hydrochloric Acid into the Fasting Specimen of Gastric Juice But Who Do Secrete It After Stimulation By Histamine.

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME C.C.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
10.	F.*	Clear, mucus.	4.0	95	2	96	90	1.6	..	2.1	tr.
	30	Clear	2.2	60	61	118	51	0.8	..	2.1	0
	60	Clear	2.2	35	62	118	52	0.7	..	2.1	0
	90	Bile "A"	6.8	20	0	102	103	0.7	..	2.1	4.2
11.	F.		3.7	10	6	111	99	1.7	..	..	..
	30		2.3	25	50	109	55	2.1	..	..	..
	60		2.4	18	37	96	53	2.4	..	..	..
12.	F.	Clear, mucus.	7.0	35	0	92	97	1.7	..	..	0.
	30	Clear	2.4	50	32	100	68	4.2	..	2.1	0.
	60	Clear	2.2	40	42	100	56	4.7	..	2.1	0
17.	F.		..	0	..	..	..	..	..	..	..
	30	Mucus ++++	..	35	30	111	71	3.6	..	..	..
	60	Mucus ++++	..	5	34	100	58	3.0	..	..	..
15.	F.	Clear	3.8	56	4	93	81	1.6	..	..	..
	30	Clear	2.6	45	12	91	77	1.8	..	..	..
	60	Clear	2.5	45	24	100	71	0.9	..	..	..
16.	F.	Clear	4.0	40	6	96	89	2.3	..	..	3.0
	30	Clear	2.0	50	30	90	56	0.7	..	..	2.0
	60	Clear	1.8	35	42	86	44	1.5	..	..	3.0
	90	Clear, mucus.	5.0	35	4	80	89	1.7	..	..	2.5
26.	F.	Clear, green.	6.8	65	0	82	91	2.4	..	..	13.3
	30	Clear, green.	1.8	70	42	95	60	1.6	..	..	15.4
	60	Tr. "B" bile.	3.1	30	14	82	65	2.3	..	..	16.0
40.	F.	Clear	7.1	18	0	80	82	2.1	..	5.9	0
	30	Clear	2.4	29	24	100	75	2.1	..	2.1	2.0
	60	Tr. "B" bile.	2.4	20	22	102	71	2.0	..	3.0	3.7
	90	Tr. "B" bile.	2.5	33	20	100	84	1.6	..	3.0	3.0
44.	F.	Clear	6.8	30	0	95	95	3.0	4.7	10.7	2.0
	30	Clear	7.3	35	0	74	78	2.5	6.6	14.5	2.0
	60	Clear	2.1	40	50	115	67	2.4	4.7	10.7	3.3
50.	F.	Bile "A"	7.8	9	0	85	90	5.4	..	..	11.2
	30	Clear	2.4	6	38	98	60	3.9	..	..	4.0
	60	Bile "A"	2.4	6	28	100	74	3.9	..	..	4.1
	90	Bile "A"	7.4	6	17	90	69	4.7	..	..	8.2
52.	F.	Mucus	6.8	2	0	..	..	..	..	..	6.0
	30	Mucus	2.8	8	22	120	98	..	..	..	4.0
	60	Mucus	..	4	16	111	95	..	..	..	5.0

*F.—Fasting or control specimen.

TABLE II (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME c.c.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_3 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
61.	F.	Mucus +++	7.9	15	0	85	90	2.3	..	..	3.5
	30	Mucus +++	2.3	5	30	..	..	2.2	..	..	2.0
	60	Mucus +++	3.4	5	8	..	..	2.3	..	..	2.0
	90	Mucus +++	7.9	15	0	73	76	2.2	..	..	3.5
73.	F.	Clear	6.8	27	0	62	68	1.9	..	..	0
	30	Clear	1.5	88	86	127	46	2.0	..	..	0
	60	Clear	1.4	54	108	155	46	1.2	..	..	0
	90	Clear	1.8	26	88	143	58	1.4	..	..	0
78.	F.	Clear, mucus.	7.9	17	0	58	60	2.3	9.0	20.2	0
	30	Clear	1.7	31	54	130	65	1.7	..	2.1	0
	60	Clear	1.6	17	70	125	58	1.5	..	2.0	0
	90	Clear	1.9	17	42	114	68	1.7	..	2.1	0
87.	F.	Blood	7.1	19	0	107	101	1.6	..	..	5.6
	30	Mucus ++++	2.4	18	18	110	90	1.3	..	..	2.0
	60	Mucus	2.2	..	38	129	90	0.8	..	..	0
	90	Blood, mucus.	2.3	8	32	..	..	..	..	..	..
89.	F.	Clear, mucus.	6.7	8	0	93	96	1.1	..	..	..
	30	Clear	2.4	25	30	105	80	1.1	..	..	..
	60	Clear	2.0	25	44	118	80	1.8	..	..	..
	90	Clear	2.6	8	25	108	80	1.2	..	..	..
95.	F.	Clear, mucus.	6.9	10	0	98	110	2.9	10.7	23.8	5.2
	30	Clear	2.4	4	..	..	..	0.8	..	1.7	0
	60	Clear	2.2	15	42	123	80	0.5	..	4.0	0
	90	Clear	2.2	15	39	135	103	0.5	..	2.1	0
102.	F.	Clear	7.0	24	0	93	109	3.0	11.0	24.6	tr.
	30	Clear	2.1	46	48	125	85	1.6	..	1.0	0
	60	Clear	1.7	28	78	141	70	1.2	..	1.0	0
	90	Clear	1.9	15	50	137	84	1.2	..	1.0	0
105.	F.		..	0	..	..	..	..	..	..	..
	30	Clear	2.0	170	38	95	60	1.3	..	2.1	0
	60	Clear	1.8	100	52	112	62	1.0	..	2.1	0
	90	Clear	1.6	80	60	117	60	1.0	..	2.1	0
119.	F.	Mucus ++++	6.8	18	0	80	88	..	..	..	..
	30	Mucus +	1.9	45	50	113	55	..	..	..	..
	60	Mucus +	1.6	57	80	127	49	..	..	..	..
	90	Mucus, Blood	1.9	90	48	96	43	..	..	..	..
120.	F.	Clear	7.6	..	0	96	93	..	..	..	..
	30	Clear	3.0	..	16	86	59	..	..	..	..
	60	Clear	2.5	..	25	88	57	..	..	..	..
	90	Clear	4.5	..	2	80	67	..	..	..	..

TABLE III

Data on Patients in Group III Who Secrete no Free Hydrochloric Acid into the Gastric Juice Either Before or After Stimulation

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME C.C.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
14.	F.*	Yellow	7.6	25	0	79	91	3.3	..	..	..
	30	Mucus	7.8	20	0	85	103	3.2	..	..	..
	60	Yellow, mucus	7.6	8	0	..	..	..	..	..	..
19.	F.	Bile tr.	6.8	42	0	62	65	2.2	..	..	..
	30	Clear	6.8	24	0	80	75	2.9	..	..	..
	90	Bile tr.	6.8	25	0	60	64	3.7	..	..	..
21.	F.	Yellow	7.4	55	0	103	117	1.6	8.5	18.9	..
	60	Clear, mucus.	6.8	5	0	127	123	1.2	..	..	..
21.	F.	Pale yellow	7.0	50	0	108	116	4.0	..	..	..
	30	Pale yellow	6.8	6	0	98	101	3.3	..	..	..
	60		..	0	..	..	..	..	..	..	..
	90	Pale yellow	6.6	26	0	88	86	2.8	..	..	..
23.	F.		7.3	8	0	83	102	3.1	..	..	..
	30		7.2	8	0	83	96	3.3	..	..	..
	60		6.7	15	0	93	95	3.4	..	..	..
	90		7.3	5	0	90	102	4.5	..	..	..
24.	F.		6.8	8	0	95	115	5.3	..	..	..
	30		6.2	3	0	..	..	4.0	..	..	13.8
	60		..	0	..	..	..	..	..	..	..
	90		5.2	7	0	75	79	3.3	..	..	8.2
25.	F.		7.4	10	0	57	50	5.3	..	..	10.9
	30		6.8	14	0	53	54	5.3	..	..	15.0
	60		3.6	12	4	65	65	6.0	..	..	4.1
	90		6.9	3	0	..	..	..	..	..	..
28.	F.	Bile "A"	7.0	30	0	103	116	5.3	..	..	5.8
	30	Tr. bile	7.6	5	0	92	100	4.3	..	..	7.8
	60	Tr. bile	7.2	15	0	102	103	4.3	..	..	8.4
	90	Bile "A"	7.0	38	0	..	..	4.4	..	..	7.8
29.	F.		7.8	30	0	115	135	3.0	..	..	0
	30		7.6	20	0	113	132	1.5	..	..	2.0
	60		..	0	..	..	..	..	..	..	..
	90		7.6	15	0	117	..	1.9	..	..	4.0
30.	F.		7.3	5	0	101	110	4.0	..	..	5.5
	30		..	2	0	..	..	..	..	..	8.0
	60		6.5	15	0	123	123	5.4	..	..	9.0
33.	F.		7.0	7	0	100	115	3.7	..	..	5.7
	30		7.4	7	0	115	116	3.0	..	..	2.0
	60		7.0	5	0	115	113	2.7	..	..	8.3

*Fasting or control specimen.

TABLE III (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME C.C.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
35.	F.		..	1	..	..	..	..	..	..	..
	30		6.6	86	0	57	67	4.9	..	..	6.3
	60		6.7	40	0	50	48	4.8	..	..	8.0
35. (90)	F.	Mucus, bile.	7.1	16	0	66	92	2.0	13.0	29.0	13.0
	30	Mucus	7.2	12	0	60	81	3.2	11.7	26.0	9.0
	60	Mucus	7.2	48	0	33	50	3.2	8.0	17.0	7.0
	90	Tr. bile	6.9	18	0	78	100	3.1	9.0	20.0	18.0
39.	F.		..	15	0	50	55	..	..	..	9.3
	30		..	5	0	38	42	..	..	..	8.0
	60		..	5	0	46	50	..	..	..	9.5
51.	F.	Bile +	7.5	6	0	100	114	5.5	5.4	12.0	0
	30	Bile +	7.3	6	0	105	119	4.0	5.8	12.6	4.0
	60	Bile tr.	7.1	9	0	122	132	2.8	5.8	12.6	5.6
55.	F.		7.9	10	0	52	54	..	..	..	5.7
	30		7.8	10	0	35	34	..	..	..	3.1
	90		8.0	8	0	42	45	..	..	..	3.5
56.	F.	Mucus ++++	7.1	8	0	87	94	..	..	..	4.0
	30	Mucus ++++	6.7	3	0	83	89	..	..	..	4.0
	60	Mucus ++++	6.7	3	0	72	78	..	..	..	4.9
	90	Mucus ++++	7.2	5	0	83	88	..	..	..	5.6
57.	F.	Mucus ++++	..	4	0	97	100	..	..	..	2.1
	30	Mucus ++++	..	4	0	97	99	..	..	..	5.6
	60	Mucus ++++	..	7	0	110	112	..	..	..	10.3
	90	Mucus ++++	..	15	0	79	80	..	..	..	10.6
58.	F.	Bile +	7.0	10	0	53	50	..	..	..	11.2
	30	Bile +	6.9	10	0	63	65	..	..	..	13.5
	60	Bile +	7.2	5	0	63	59	..	..	..	11.6
	90	Bile +	6.7	10	0	81	81	..	..	..	11.6
58.	F.	Clear	8.4	13	0	33	40	1.1	..	..	3.5
	30	Bile +	7.2	20	0	57	60	1.6	..	..	18.5
	60	Bile +	7.2	22	0	78	75	2.1	..	..	16.5
	90	Clear	7.9	16	0	107	109	1.8	..	..	14.6
59.	F.	Clear	7.0	14	0	56	57	..	..	..	12.0
	30	Bile +	7.0	7	0	58	60	..	..	..	9.0
	60	Bile +	7.0	6	0	86	88	..	..	..	..
	90	Bile +	7.0	6	0	103	102	..	..	..	9.8
60.	F.		7.3	15	0	63	60	3.4	..	..	..
	30		6.7	7	0	61	58	3.4	..	..	..
	60		6.2	15	0	60	61	3.4	..	..	..

TABLE III (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME c.c.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
64.	30		3.5	22	8	66	63	5.6	..	..	..
	60		..	22	0	47	50	5.2	..	..	..
68.	F.		7.9	19	0	90	98	3.4	..	..	5.6
	30		7.9	8	0	93	103	2.6	..	..	7.6
	90		..	4	0	..	..	3.4	..	..	11.2
79.	F.	Clear	7.9	14	0	92	99	4.4	..	..	tr.
	30	Clear	7.9	19	0	73	116	4.1	..	..	tr.
	60	Bile +	7.9	21	0	83	110	4.1	..	..	tr.
	90	Bile +++	7.8	14	0	90	105	4.4	..	..	12.3
77.	F.	Light bile +	7.9	18	0	75	77	3.6	..	..	..
	30	Light bile +	6.9	41	0	98	99	4.1	..	..	..
	60	Light bile +	7.1	47	0	91	94	3.1	..	..	..
	90	Bile +++	7.8	19	0	90	91	2.9	..	..	..
83.	F.	Mucus ++++	7.2	17	0	90	92	2.4	..	..	..
	30	Mucus ++++	7.2	24	0	92	94	2.4	..	..	..
	60	Light bile	6.9	20	0	95	95	1.3	..	..	..
	90	Mucus ++++	6.7	15	0	99	102	..	..	..	..
86.	F.	Mucus	8.4	3	0	..	..	..	..	..	..
	30	"B" bile	7.0	7	0	116	119	1.9	..	..	16.9
	60	Blood, mucus.	7.3	9	0	130	132	2.7	..	..	..
88.	F.	Bile tr.	7.1	16	0	110	121	2.2	11.6	25.8	9.0
	30	Bile tr.	7.1	10	0	105	114	2.2	9.9	21.7	8.0
	60	Bile tr.	7.9	12	0	105	117	2.1	12.5	27.7	11.0
	90	Bile tr.	7.9	18	0	100	117	1.6	12.5	27.7	13.0
97.	F.	Bile tr.	7.0	10	0	50	65	2.8	12.3	27.0	..
	30	Bile +	7.0	15	0	57	66	2.8	10.7	24.0	..
	60	Bile +	6.7	12	0	60	62	3.1	6.7	15.0	..
	90	Clear	6.7	13	0	55	59	2.6	5.8	13.0	..
107.	F.	Clear	7.2	10	0	113	120	2.9	7.0	15.5	..
	60	Bile tr.	3.7	14	12	131	125	0.7	8.7	19.2	..
	90	Bile tr.	7.2	11	0	111	120	1.5	5.7	12.6	..
108.	F.	Bile +	8.3	52	0	100	109	2.7	24.6	52.2	..
	60	Bile +	8.5	22	0	108	118	1.4	23.0	50.4	..
109.	F.	Bile tr.	6.8	20	0	103	112	0.9	..	2.1	..
	30	Bile tr.	5.8	20	9	113	114	0.8	..	2.1	..
	60	Bile tr.	5.9	15	11	120	124	0.9	..	1.0	..
	90	Bile tr.	6.8	30	0	112	130	1.4	..	1.1	..
110.	F.	Clear, mucus.	6.7	15	0	108.	113	1.9	5.7	12.6	..
	60	Clear, mucus.	7.1	15	0	137	140	1.4	4.7	10.7	..

TABLE III (Continued)

CASE NO.	TIME MINUTES	DESCRIPTION	pH	VOLUME C.C.	FREE HCl	TOTAL CHLORIDES AS CHLORIDE ION	BASE	P AS PHOSPHATE ION	CO_2 AS HCO_3 ION	CO_2 VOLUMES %	TRYPSIN UNITS
					MILLIEQUIVALENTS PER LITER						
111.	F.	Bile tr.	2.4	12	0	102	118	2.5	8.3	18.3	..
	30	Bile tr.	7.7	6	0	97	103	1.9	6.5	14.5	..
	90	Bile tr.	..	18	0	100	46?	2.0	4.8	10.7	..
112.	F.	Clear	8.4	60	0	70	112	3.1	30.0	67.3	..
	30	Clear	7.8	45	0	68	95	1.9	21.9	48.5	..
	60	Clear	7.6	30	0	108	112	2.7	17.0	38.1	..
	90	Clear	7.7	35	0	93	106	2.2	17.5	39.0	..
121.	F.	Clear	6.9	3	0	..	..	..	..	..	..
	30	Clear	5.9	4	0	68	72	..	..	..	..
	60	Clear	6.8	10	0	56	65	..	..	..	..
	90	Clear	6.8	10	0	43	61	..	..	..	..
122.	F.	Mucus	6.5	..	0	58	95	..	..	..	..
	30	Mucus	7.1	..	0	60	90	..	..	..	..
	60	Mucus	6.9	..	0	67	95	..	..	..	..
	90	Mucus	6.3	..	0	86	89	..	..	..	..
123.	F.	Clear	7.7	16	0	70	87	2.1	..	..	0
	30	Bile tr.	7.4	10	0	90	96	2.8	..	..	0
	60	Clear	6.7	6	0	122	123	2.1	..	..	0
	90	Bile +	6.7	8	0	112	120	3.3	..	..	0
124.	F.	Mucus +++	7.4	11	0	72	94	4.1	19.0	42.7	..
	30	Mucus +	7.6	12	0	80	97	4.3	14.3	31.6	..
	60	Mucus +	7.7	14	0	67	82	4.3	10.3	23.0	..
	90	Mucus ++++	7.7	9	0	62	85	4.3	10.6	23.6	..
125.	F.	Clear, mucus.	7.4	..	0	64	93	..	..	..	0
	30	Clear, mucus.	7.0	..	0	55	60	..	..	..	0
	60	Clear, mucus.	7.2	..	0	70	80	..	..	..	0
	90	Mucus, bile.	7.4	..	0	73	95	..	..	..	0
126.	F.	Clear	..	30	0	73	83	4.2	..	..	0
	30	Clear	..	40	0	75	80	5.0	..	..	0
	60	Clear	..	6	0	90	98	5.0	..	..	6.8
	90	Clear	..	13	0	112	128	4.6	..	..	tr.
127.	F.	Clear	7.6	12	0	99	112	3.0	9.5	21.0	..
	30	Clear	7.1	14	0	85	94	2.7	6.4	14.0	..
	60	Bile tr.	6.8	25	0	99	103	3.4	5.4	12.2	..
	90	Bile tr.	7.4	8	0	105	115	3.9	4.4	9.9	..

TABLE IV

Computation of the percentage of HCl and NaCl in extracted specimens. From this is figured the strength at which these chemicals have originated in pure solution and the amount of that solution in c.c. The calculation is given on page 18.

Case No.	Time minutes	Volume c.c.	Milliequivalents HCl	Cl–	Base	Specimen percentage HCl	NaCl	Volume in c.c. HCl	NaCl	Secretion concentration HCl	NaCl
8.	F.	30	24	88	65	.086	.377	8.1	21.9	.320	.515
	30	100	74	120	45	.266	.261	62.2	37.8	.428	.690
	60	95	85	136	40	.306	.232	64.6	30.4	.450	.725
	90	55	86	130	40	.309	.232	37.5	17.5	.453	.730
10.	F.	90	2	96	90	0	.522	0	90.0	0	.522
	30	60	61	118	51	.220	.296	32.1	27.9	.407	.650
	60	35	62	118	52	.228	.302	19.0	16.0	.407	.650
	90	20	0	102	105	0	.608	0	20.0	0	.608
23.	F.	8	0	83	102	0	.592	0	8.0	0	.592
	30	8	0	83	96	0	.556	0	8.0	0	.556
	60	15	0	93	95	0	.551	0	15.0	0	.551
	90	5	0	90	102	0	.592	0	5.0	0	.592
31.	F.	190	46	113	70	.166	.406	75.3	114.7	.417	.673
	30	150	112	151	46	.403	.267	106.3	43.7	.567	.916
	60	32	100	148	52	.360	.302	21.0	11.0	.547	.881
	90	27	90	147	62	.324	.359	16.0	11.0	.547	.881
40.	F.	18	80	80	82	0	.475	0	18.0	0	.475
	30	29	24	100	75	.086	.434	7.4	21.6	.360	.580
	60	20	22	102	71	.079	.415	4.4	15.6	.367	.590
	90	33	20	100	84	.070	.487	16.6	16.4	.360	.580
44.	F.	30	0	95	95	0	.552	0	30.0	0	.552
	30	35	0	74	78	0	.454	0	35.0	0	.454
	60	40	50	115	67	.180	.388	17.1	22.9	.422	.667
56.	F.	8	0	87	94	0	.545	0	8.0	0	.545
	30	3	0	83	89	0	.515	0	3.0	0	.515
	60	3	0	72	78	0	.453	0	3.0	0	.453
	90	5	0	83	88	0	.510	0	5.0	0	.510
58.	F.	13	0	33	40	0	.232	0	13.0	0	.232
	30	20	0	57	60	0	.348	0	20.0	0	.435
	60	22	0	78	75	0	.435	0	22.0	0	.435
	90	16	0	107	109	0	.632	0	16.0	0	.632
73.	F.	27	0	62	68	0	.395	0	27.0	0	.395
	30	88	86	127	46	.309	.267	57.3	30.7	.476	.765
	60	54	108	155	46	.288	.267	37.9	16.1	.526	.894
	90	26	88	143	58	.313	.336	14.7	10.7	.555	.846
78.	F.	17	0	58	60	0	.348	0	17.0	0	.348
	30	31	54	130	65	.194	.376	14.0	17.0	.429	.690
	60	17	70	125	58	.257	.334	9.3	7.7	.461	.742
	90	17	42	114	68	.151	.394	6.5	10.5	.396	.638
79.	F.	55	30	103	75	.108	.435	15.7	39.3	.378	.609
	30	86	73	132	60	.263	.348	47.2	38.3	.479	.772
	60	36	46	122	75	.166	.435	12.9	21.1	.436	.707
	90	40	24	96	75	.086	.435	9.7	30.3	.356	.575
98.	F.	45	10	83	75	.036	.435	5.3	39.7	.306	.493
	30	70	70	121	50	.252	.290	40.8	29.2	.432	.696
	60	50	52	121	68	.187	.394	21.7	28.3	.432	.696
	90	30	28	108	82	.101	.475	7.6	22.4	.396	.637

TABLE IV (Continued)

Case No.	Time minutes	Volume c.c.	Milliequivalents HCl	Cl–	Base	Specimen percentage HCl	NaCl	Volume in c.c. HCl	NaCl	Secretion concentration HCl	NaCl
102.	F.	24	0	93	109	0	.540	0	24.0	0	.540
	30	46	48	125	85	.177	.494	16.6	29.4	.479	.761
	60	28	78	141	70	.280	.406	14.8	13.2	.533	.858
	90	15	50	137	84	.180	.488	5.6	9.4	.483	.767
113.	F.	63	8	103	92	.029	.530	5.0	58.0	.370	.598
	30	47	26	100	76	.093	.441	12.0	35.0	.360	.580
	60	130	58	111	53	.290	.307	67.8	62.2	.400	.643
	90	90	48	105	51	.173	.295	43.2	46.8	.379	.609

TABLE V

Data to Demonstrate that NaCl Is not Secreted at a Constant Level.

Case No.	Time minutes	Volume c.c	HCl meq.	Cl– meq.	Base meq.	Specimen percentage of NaCl: As found	If secretion strength had remained at pre-stimulated level and had been secreted in pure solution	Secretion concentration according to formula for NaCl
102.	F.	24	0	93	109	.540	.540	.540
	30	46	48	125	85	.494	.345	.761
	60	28	78	141	70	.406	.281	.858
	90	15	50	137	84	.488	.339	.767
73.	F.	27	0	62	68	.395	.395	.395
	30	88	86	127	46	.267	.138	.765
	60	54	108	155	46	.267	.117	.894
	90	26	88	143	58	.336	.156	.846

REFERENCES

[1]GAMBLE, J. L., and MCIVER, M. A.: Fixed base in gastric juice, Proc. Soc. Exper. Biol. and Med., 1925-26, xxiii, 439.

[2]MACLEAN, H., and GRIFFITHS, W. J.: The automatic regulation of gastric acidity, Jr. Physiol., 1928, lxvi, 356.

[3]MACLEAN, H.; GRIFFITHS, W. J., and HUGHES, T. A.: The relationship of peptic activity to neutral chloride secretion during gastric digestion in man, Jr. Physiol., 1929, lxvii, 409.

[4]BOLDYREFF, W.: The self-regulation of the acidity of the gastric contents and the real acidity of the gastric juice, Quart. Jr. Exper. Physiol., 1915, viii, 1.

[5]MACLEAN, H., and GRIFFITHS, W. J.: The factors influencing the concentration of hydrochloric acid during gastric digestion, Jr. Physiol., 1928, lxv, 63.

[6]BULGER, H. A.; STROUD, C. M., and HEIDEMAN, M. L.: Studies of the chemical mechanism of hydrochloric acid secretion. I. Electrolyte variations in human gastric juice, Jr. Clin. Invest., 1927-28, v, 547.

[7]POLLAND, W. S.; ROBERTS, A. M., and BLOOMFIELD, A. L.: The chloride, base and nitrogen content of gastric juice after histamine stimulation, Jr. Clin. Invest., 1927-28, v. 611.

[8]BLOOMFIELD, A. L.; ROBERTS, A. M., and POLLAND, W. S.: The composition of

the gastric secretion in cases of anacidity, Trans. Assoc. Am. Phys., 1928, xliii, 242.

[9]Clark, W. M.: The determination of hydrogen ions, Third Edition, 1928, Williams and Wilkins, Baltimore.

[10]Van Slyke, D. D.: The determination of chlorides in blood and tissues. Jr. Biol. Chem., 1923, lviii, 523.

[11]Stadie, W. C., and Ross, E. C.: A micromethod for the determination of base in blood and serum and other biological materials, Jr. Biol. Chem., 1925, lxv, 735.

[12]Benedict, S. R., and Theis, R. C.: A modification of the molybdic method for the determination of inorganic phosphorus in serum. Jr. Biol. Chem., 1924, lxi, 63.

[13]Van Slyke, D. D., and Cullen, G. E.: Studies of acidosis. I. The concentration of the blood plasma; its significance and its determination as a measure of acidosis, Jr. Biol. Chem., 1927, xxx, 289.

[14]Martin, L.: Biliary, pancreatic and duodenal studies. II. Estimation of pancreatic enzymes and value of such determinations from a clinical standpoint, Arch. Int. Med., 1927, xxxix, 343-355.

[15]Michaelis, L.: Some problems concerning the gastric juice, Harvey Lectures, 1926-27, xxii, 59.

[16]Van Slyke, D. D.; Hastings, A. B.; Hiller, A., and Sendroy, J., Jr.: Studies of gas and electrolyte equilibria in blood. XIV. The amounts of alkali bound by serum albumin and globulin, Jr. Biol. Chem., 1928, lxxix, 769.

The First Aphorism of Hippocrates*

By George Dock, M.D., Sc.D., F.A.C.P., *Pasadena, Calif.*

We all claim descent, as physicians, from the philosophers and physicians of the great period of Greek civilization, the fifth century, B.C., and yet in the rapid increase of current literature we may easily forget what that means. Of course, we can easily revive our knowledge in any of a number of excellent works on Medical History, old or new; or, we can reread any chapter or number of chapters in the Hippocratic Writings. In the following I have chosen one book, namely, the Aphorisms, and traced it down through the centuries, at long intervals, to be sure, seeing how it was reflected by the mind of the most brilliant Greek physician of Pergamos and Rome in the second century, A.D.; by some outstanding Arabs of the ninth, tenth and eleventh centuries; a keen and practical Englishman of the fourteenth century; and then through the busy days of early book-printing down to our own time. Ancient and modern critics agree that a great deal, at least, of the Book of Aphorisms is the work of Hippocrates himself, although admitting that additions and alterations have been made. The earliest commentator we know, Galen, believed Hippocrates produced the Aphorisms in his old age, and as one of the latest commentators, Francis Adams, has said, no one could have written them but one who had long been familiar with the phenomena of disease, and had maturely reflected on all the various subjects to which the Aphorisms relate. That the work was highly valued in the centuries immediately following the lifetime of the author we can gather from the fact that it was taken up by the School of Alexandria, where it was codified and preserved, and in time reached Galen, who, with characteristic enthusiasm and energy arranged the Book of Aphorisms in seven sections, added his own Commentaries and so enabled it to come down through the Dark Ages and not only survive the downfall of Galenism but be used as a text-book up to the time of the discoveries of Percussion and Auscultation, and of the Cell. The characters of the two men, Hippocrates and Galen, have been vividly analyzed recently by Charles Greene Cumston.*

The next name that comes down to us with that of Hippocrates is Hunain, or Honein ben Ishak, a Nestorian Christian better known as Joannitius, born about 809 A.D., in a village in Mesopotamia, and the most learned among the translators from Greek into

*Presented at the San Francisco Meeting of the American College of Physicians, April 4, 1932.

*"Histoire de la Medecine," Paris, 1931.

Arabic. Joannitius was the author of one of the most celebrated "Isagoges", or Introductions to Medicine. Used in the Middle Ages as textbooks in manuscript, these were highly regarded and were therefore among the earliest medical books to be reproduced by printing. I have been fortunate enough to examine a very good example in the library of Dr. LeRoy Crummer. Spelling, capitals and abbreviations show the influence of manuscript methods. The title is: "Ysagoge Johannici / Incipiunt Ysagoge Joannici / adtegni galien." The place of publication was probably Lyons, the date 1510. Like other similar works, this contains the "Libri afforismorum domini Ypocratis", in Latin, translated from the Greek by Theodorus Gaza, "medicus". Some of the Introductions had the title "Articellâ", or "Artisella", from the fact that they contained the "ars parva" of Galen, also called the "Techni" or "Tegni" in various copies, and not from "Artis cella" as sometimes thought. "Artesela" was the title of a Venetian imprint of 1491. Dr. Crummer has a good example printed in Florence in 1534.

That remarkable character, Suidas, a Greek biographer and lexicographer, who lived in the end of the tenth century, spoke of the Aphorisms as surpassing the human mind. An Arab version bearing the date 1100 A.D. is thought to have been the most ancient manuscript on linen paper, parchment and papyrus having been used before. The statement shows how scholars habitually ignored the Chinese, for they used paper from the second century, B.C. The Arabs came into possession of some in 751, when a Chinese army attacked Samarkand, and paper-making then spread all through Arabic lands and thence to Europe. It is said that the oldest recorded Western document on paper is a deed of King Roger of Sicily, in 1102.

Constantine, called the African, one of the ornaments of the School of Salerno, where he became a monk, translated the Aphorisms with the Commentaries of Galen into Latin late in the eleventh century, this being the first work of Galen to be put into Latin. Rabbi Moses Maimonides, born in Cordova in 1135, called The Great Maimonides, and better known as philosopher and Talmudist than physician, included in his writings a Commentary on the Aphorisms.

How vital the Aphorisms were in the education of the medieval medical student we can see by a conspicuous example. John of Gaddesden, supposed by some to have been the original of "The Doctour of Phisyk" of the "Canterbury Tales", studied medicine at Oxford about 1303. For "inception in medicine", which apparently included the taking of the B.M. degree at that time, he had to have read one book of Galen or one book of the Aphorisms of Hippocrates. So well did John study the aphorisms that he quoted them one hundred and twenty times in his great work, the "Rosa Anglica", written in 1314. A System of Medicine "from head to feet", this was widely used in manuscript in the fourteenth and fifteenth centuries. There are three copies in the British Museum; one, dated 1356, in the Bibliotheque Nationale in Paris, and one

each in the Bodleian and in Merton College library. It was printed in 1492 (Pavia); 1502 (Venice); 1517 (Pavia); 1595 (Augsburg).* The "Surgery" of Guy de Chauliac, father of French surgery and most celebrated surgeon of the middle ages, first published in 1363, also shows familiarity with the Aphorisms. In the great medieval medical schools of Salerno and Montpellier, Hippocrates and Galen were the two authors whose works were especially studied. Salerno, indeed, was called Civitas Hippocratica.

Two and a half centuries after Gaddesden, we find the youthful Felix Plater, who became one of the best observers and one of the most judicious writers of the sixteenth century, studying for the doctorate in Basel. When he took his final examinations in 1557, he was called upon to explain, among other questions, an aphorism of Hippocrates, (the first in section three) reading: "Mutationes temperum pariunt morbos".** Another century later, about 1647, Sir Thomas Browne advised a correspondent "that Hippocrates' Aphorisms should be conned for the frequent use which may be made of them." (Pickering Ed., 1836.)

The editions of the Aphorisms before 1500 are not accurately known. After 1500, and including those in "Complete Works" of Hippocrates and of Galen, in Isagoges and Articellas, the number is so large that some writers think the Aphorisms have been printed oftener than any other profane work. A.-J.-L. Jourdan and F.-G. Boisseau, in the Dict. des Sci. Méd., Biographie Médicale, Art. Hippocrate, T. 5, Paris, 1822, give forty editions between 1532 and 1800.

J.-E. Dezeimeris, Dict. Hist. de la Médecine, anc. et mod. T. III., Paris, 1836, gives a still larger number of editions, including many incunables, and also including Articellas, and combinations of various works, Hippocratic and others, with the Aphorisms. He mentions fourteen French versions up to 1835, and 27 versified paraphrases, chiefly Latin. The number of Commentaries on the Aphorisms, as Dezeimeris says, is immense, and he names many in his very interesting article. The greatest number of "Aphorisms" I find in a single list is that in the Catalogue of Printed Books of the British Museum, 1889, viz., 134 editions of the Aphorisms as separate works. Many languages are represented including Greek, Arabic, Latin, Italian, Spanish, Hebrew, English and French. Of Greek and Latin texts, there were 13 in the sixteenth century; 19 in the seventeenth; 6 in the eighteenth, 1 in the nineteenth: Greek and English, one in 1831: in Latin only, 5 in the fifteenth century; 29 in the sixteenth; 29 in the seventeenth; 10 in the eighteenth: Latin and French, 3 in the seventeenth century: French only, 1557, 1660, 1685: Italian only, 1621; English, 1550, 1585, 1610, 1655, 1663, 1708, 1735: in German; 1825, 1860. An Arabic text of Honain ben Ishak was printed in Calcutta in 1832. But this number is incomplete, and an effort to correct it from bibliographies

*H. P. Cholmeley, John of Gaddesden and the Rosa Anglica. Oxford. 1912.

**Brief Notes on Felix Plater, with Extracts from his ms. Memoirs preserved in the Library of Basel. By C. G. Cumston, Johns Hopkins Hosp. Bull., April, 1912.

does not seem worth while. The many versified translations suggest that it was probably a popular pastime in the early years of the revival of learning to turn the Greek prose into Latin verse, or rarely a modern language. The places of publication include all the well-known seats of printing. The number of editions depended to a great extent on the free-trade in printing, especially that dealing with copies of the classics, in the original tongues as well as in Latin translations.

In size, we have everything from quarto to 32mo, pocket sizes being numerous from the earliest printing. The editors include all the great restorers and commentators of Greek medicine. One of the most celebrated, although better known at present as a comic writer than a medical guide, was Francois Rabelais, the biographer of Gargantua and Pantagruel. His talents were well known to his contemporaries. Familiar with Greek, Latin and Arabic, made bachelor at Montpellier in 1530, he lectured on Galen and Hippocrates in 1531. Dr. A. F. Le Double (Rabelais Anatomiste et Physiologiste, Paris, 1899) has shown the extent and accuracy of his anatomical knowledge. Gargantua began to appear in 1533, but in the preceding year Rabelais had published a Greek edition of the Aphorisms, and in 1543 and 1545 he published Latin versions of the latter from the translation of Nicholas Leoniceno. Dr. LeRoy Crummer has a very fine example of the very rare Ionic text (1532), bound with the Aphorisms (1545) and three other Hippocratic chapters and the Ars medicinalis of Galen. Many of the editions of the sixteenth and seventeenth centures included the Commentaries of Galen. A careful study of the latter might explain the disinclination to original work so evident in students of those days. Besides the seven sections of Galen, almost universally followed, there was sometimes an eighth, containing Aphorisms thought to be apocryphal.

The lack of classification is remarkable, and Dezeimeris rearranged the Aphorisms according to a simple clinical classification, which I shall follow in making some selections, using the edition of 1841. The English text of Francis Adams (Sydenham Society, London, 1849), the scholarly surgeon of Banchory, the French of E. Littre (Paris, 1844), and the German of Robert Fuchs (Munich, 1893) are convenient for modern readers.

My early studies of the Aphorisms


APHORISMO
RVM HIPPOCRATIS
SECTIONES
SEPTEM,
Ex Franc. Rabelæſi
recognitio-
ne.
Quibus ex Ant. Muſæ Commentariis adiecimus & Octauam : & quardam alia, quæ ſequens indicabit pagella.
VIRTVTE DVCE, COMITE FORTVNA.
APVD SEB. GRY-
PHIVM LV-
GDVNI,
1545.

FIG. 1. Title page of 1545 Aphorisms, edited by Rabelais, from specimen in the collection of Dr. LeRoy Crummer.

were made in a few examples I happened to have in my own collection. When I took up the matter more seriously, I extended the search, until I had examined more than fifty examples. It is a pleasure to thank various libraries and individuals who have assisted me. I am especially grateful to Lane Library, San Francisco, where there is a very interesting collection of Hippocratic material. The Huntington Library, Pasadena, has two very rare editions of the Aphorisms, and I am also indebted to that library for the use of its reference material. The Barlow Library of Los Angeles, has been of great assistance. I have already mentioned my indebtedness to Dr. LeRoy Crummer, but should include the interest and the extensive bibliographic knowledge of Mrs. Crummer. After I had covered the ground fairly thoroughly, I took advantage of the kindness and skill of Dr. W. W. Francis, librarian of the Osler Library of McGill University, Montreal. Dr. Francis made copies of the First Aphorism in all the early specimens in that great collection, and also many extracts from commentaries, and added many suggestions of his own.


APHORISMES
D'HIPPOCRATES,
AVEC LE COMMENTAIRE
DE GALIEN SVR LE
premier Liure.
Traduits de Grec en François,
Par M. I. Breche.
Autre Annotations sur ledit premier Liure: consistãt en certaines Paraphrases formans de brief commentaire, depuis le second Liure iusques à la fin du septiesme, par ledit Breche.
PLVS
Les Aphorismes de I. de Damascene, Medecin Arabe: Ensemble vne Epitome sur les trois Liures des Temperamens de Galien.
A ROVEN,
Chez ROMAIN DE BEAVVAIS, pres le grand portail nostre Dame.
1606.

FIG. 3. Title-page of Latin-Greek Aphorisms edited by Jean Breche, of Tours. Rouen, 1606.

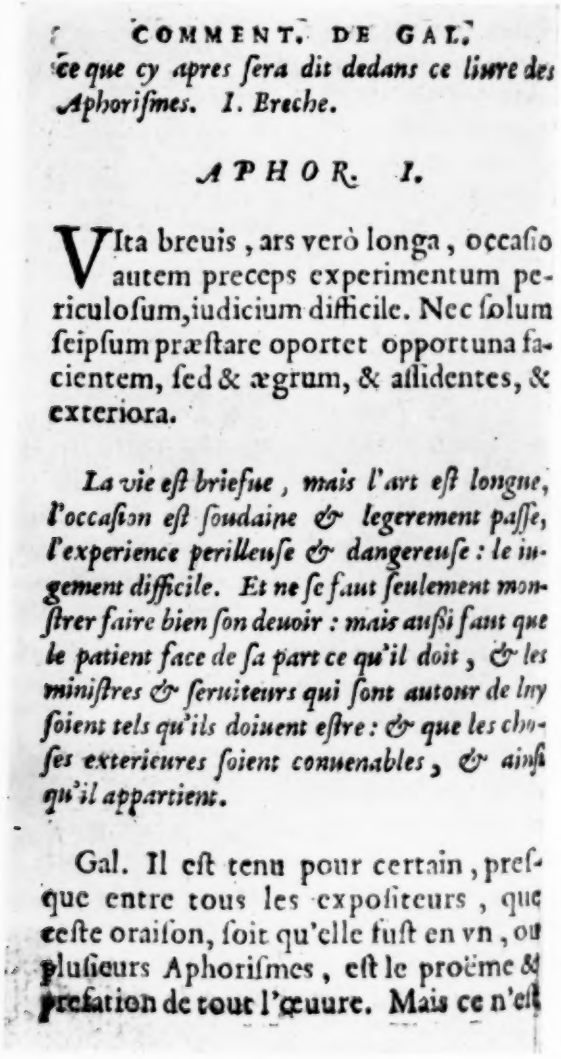

ΙΠΠΟΚΡΑ.
ΤΟΥΣ ΑΦΟΡ
ΡΙΣΜΟΙ.
Τμῆμα πρῶτον.

FIG. 2. First page of Ionic Greek text of the Aphorisms, edited 1532 by Rabelais, bound with No. 1 and other Hippocratic writings.

I can think of no more striking evidence of the cleavage between ancient and modern medicine than the use of the Aphorisms up to about one hundred years ago and their neglect now. I may therefore be pardoned if I give a brief account of the work before going on to the real subject I have chosen. I shall follow the translation of Adams, at the same time expressing to his Shade the gratitude I feel for his self-sacrificing labors, all the more generous because he realized that each previous attempt to "confer upon this great work its proper position in the

English literature of medicine has proved a complete failure".

Of the numerous definitions of an aphorism, I think one of the best is Adams' version of Galen's, viz., "a writing remarkable for brevity and point". Brevity is a constant feature of the Hippocratic writings, and in the Aphorisms this has been carried so far that none of the commentators has been able to follow the example. As to the object of the work, I accept the suggestion made by many others, that it was intended to be a comprehensive treatise on the physical science, physiology and medicine known at that time. This explains the inclusion of the aphorisms about seasons,



COMMENT. DE GAL.

ce que cy apres ſera dit dedans ce liure des Aphoriſmes. I. Breche.

APHOR. I.

VIta breuis, ars verò longa, occaſio autem preceps experimentum periculoſum, iudicium difficile. Nec ſolum ſeipſum præſtare oportet opportuna facientem, ſed & ægrum, & aſſidentes, & exteriora.

La vie eſt briefue, mais l'art eſt longue, l'occaſion eſt ſoudaine & legerement paſſe, l'experience perilleuſe & dangereuſe: le iugement difficile. Et ne ſe faut ſeulement monſtrer faire bien ſon deuoir: mais auſſi faut que le patient face de ſa part ce qu'il doit, & les miniſtres & ſeruiteurs qui ſont autour de luy ſoient tels qu'ils doiuent eſtre: & que les choſes exterieures ſoient conuenables, & ainſi qu'il appartient.

Gal. Il eſt tenu pour certain, preſque entre tous les expoſiteurs, que ceſte oraiſon, ſoit qu'elle fuſt en vn, ou pluſieurs Aphoriſmes, eſt le proëme & prefation de tout l'œuure. Mais ce n'eſt

FIG. 4. Page containing the first Aphorism, from No. 3.

and the nature of waters, while the parts on the symptoms, prognosis and treatment are appropriate. There are about four hundred separate aphorisms, some of them expressing truths that twenty-three centuries confirm, and others reflecting errors handed down from the infancy of anatomy and physiology. The wealth of material goes far to explain the great regard in which the work was held in the Hippocratic dawn of medicine, as well as in the urge of the Renascence, while the far greater bulk and the ever-growing complexity of post-Harveyan medicine removed the primitive advantage, and in time made the Aphorisms unnecessary, if not practically useless. I think, however, that the undergraduate in his first vision of clinical medicine, still more, the interne, might gain much pleasure, and perhaps get an intellectual stimulus from an occasional perusal of this early work, and perhaps be led to a more serious study of other chapters of ancient medicine.

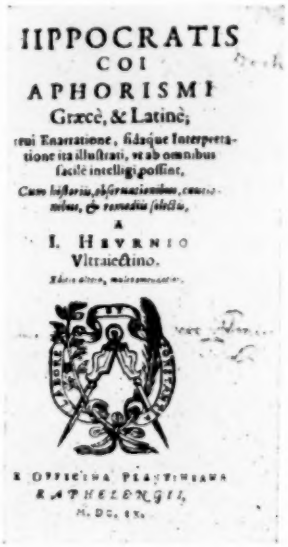
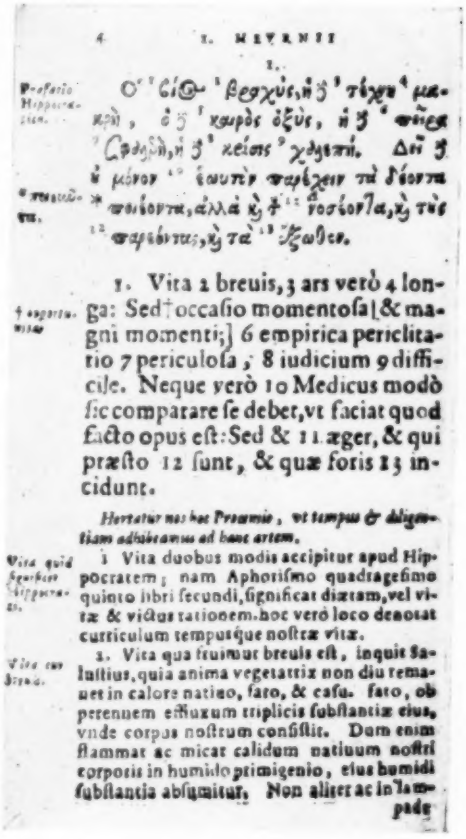

HIPPOCRATIS
COI
APHORISMI
Græcè, & Latinè,
cui Enarratione, fidáque Interpretatione ita illustrati, vt ab omnibus facilè intelligi possint.
Cum historijs, observationibus, consectariis, & remediis selectis.
A
I. HEVRNIO
Vltraiectino.
OFFICINA PLANTINIANA
RAPHELENGII,
M. DC. IX.

FIG. 5. Title page of Greek-Latin edition of the Aphorisms by Jean Heurnius, 1609.


4 I. HEVRNII

1.

Ὁ βίος βραχὺς, ἡ δὲ τέχνη μακρὴ, ὁ δὲ καιρὸς ὀξὺς, ἡ δὲ πεῖρα σφαλερὴ, ἡ δὲ κρίσις χαλεπή. Δεῖ δὲ οὐ μόνον ἑαυτὸν παρέχειν τὰ δέοντα ποιέοντα, ἀλλὰ καὶ τοὺσιν, καὶ τοὺς παρέοντας, καὶ τὰ ἔξωθεν.

1. Vita 2 breuis, 3 ars verò 4 longa: Sed occasio momentosa [& magni momenti;] 6 empirica periclitatio 7 periculosa; 8 iudicium 9 difficile. Neque verò 10 Medicus modò sic comparare se debet, vt faciat quod facto opus est: Sed & 11 æger, & qui præsto 12 sunt, & quæ foris 13 incidunt.

Hortatur nos hoc Prooemio, vt tempus & diligentiam adhibeamus ad hanc artem.

Vita quid sapiens Hippocrates.

2 Vita duobus modis accipitur apud Hippocratem; nam Aphorismo quadragesimo quinto libri secundi, significat diætam, vel vitæ & victus rationem: hoc verò loco denotat curriculum temporisque nostræ vitæ.

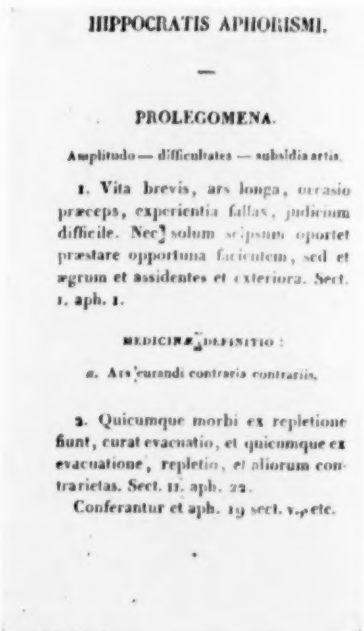
Vita cur brevis.

2. Vita qua fruimur breuis est, inquit Salustius, quia anima vegetatrix non diu remanet in calore natiuo, fato, & casu. Fato, ob perennem effluxum triplicis substantiæ eius, vnde corpus nostrum consistit. Dum enim flammat ac micat calidum natiuum nostri corporis in humido primigenio, eius humidi substantia absumitur. Non aliter ac in lampade

FIG. 6. The First Aphorism from No. 5. Compare the Greek text with that of No. 2.

The First Aphorism serves as an Introduction, or Prolegomenon, in the edition of Dezeimeris, and as I wish to give it special attention, I pass on to another often alluded to (Section II. Aph. 22): "Diseases which arise from repletion are cured by depletion; and those that arise from depletion are cured by repletion; and in general diseases are cured by their contraries". This is sometimes mentioned as the original "contraria contrariis curant-

ur", but the idea is better expressed in another Hippocratic work: "On the Places in Man". It does not seem to require any discussion now. Under the sub-title, "The Art of imitating the curative processes of Nature", we find, I. 21: "Those things which require to be evacuated should be evacuated, wherever they most tend, by the proper outlets". Cosmetics and general prognosis join in II. 54: "Largeness of person in youth is noble and not unbecoming, but in old age it is inconvenient and worse than a smaller stature". Signs of imminence of disease may be represented by II. 5: "Spontaneous lassitude indicates disease". Uroscopy has eight aphorisms relating to it, VII. 34 being one of the most interesting: "When bubbles settle on the surface of the urine, they indicate disease of the kidneys". If this means bubbles that remain after shaking the urine, from albumin in the latter, we can only wonder how such knowledge can be explained without experience with autopsies. It seems to represent a different kind of observation from that in II. 33: "In every disease it is a good sign when the patient's intellect is sound, and he is disposed to take whatever food is offered to him; but the contrary is bad". Equally sage is II. 19: "In acute disease it is not quite safe to prognosticate either death or recovery". And II. 42: "It is impossible to remove a strong attack of apoplexy, and not easy to remove a weak one". In V. 10, we may not agree with the time element, but the general thought is suggestive: "Persons who escape an attack of quinsy, when the disease is turned upon the lungs, die in seven days; or if they pass these they become affected with empyema". That Hippocrates was far in advance of his time in his knowledge of pleural disease is generally known. A good example is shown in VII. 44: "When empyema is treated either by the cautery or incision, if pure and white pus flows from the wound, the patients recover; and if mixed with blood, slimy and fetid, they die". VI. 27: "Those cases of empyema which are treated by incision or the cautery, if the water or pus flows rapidly all at once, certainly prove fatal". An interesting statistical observation is given in V. 9: "Phthisis most commonly occurs between the ages of eighteen and thirty-five". V. 12 is not so clear: "Phthisical persons, the hair of whose head fall off, die if diarrhoea set in".



HIPPOCRATIS APHORISMI.

—

PROLEGOMENA.

Amplitudo — difficultates — subsidia artis.

1. Vita brevis, ars longa, occasio præceps, experientia fallax, judicium difficile. Nec solum seipsum oportet præstare opportuna facientem, sed et ægrum et assidentes et exteriora. Sect. 1. aph. 1.

MEDICINÆ DEFINITIO:

a. Ars curandi contraria contrariis.

2. Quicumque morbi ex repletione fiunt, curat evacuatio, et quicumque ex evacuatione, repletio, et aliorum contrarietas. Sect. II. aph. 22.

Conferantur et aph. 19 sect. v. etc.

FIG. 7. From J.-E. Dezeimeris' Résumé de la Médecine Hippocratique, ou Aphorismes d'Hippocrate classé dans un ordre systématique, etc. Paris, 1841.

The doctrine of critical days is a serious difficulty in Hippocratic writings. A good example, in the sense that it is hard to understand, is IV. 64: "When in cases of fever jaundice occurs on the seventh, the ninth, the eleventh, or the fourteenth day, it is a good symptom, provided the hypochrondriac region be not hard. Otherwise it is not a good symptom". The very important doctrine of crises has a good example in II. 12: "What remains in disease after the crisis is apt to produce relapses", but II. 23 seems more dogmatic than useful: "Acute diseases come to a crisis in fourteen days", unless we accept the explanation that we have here a definition of an acute disease. II. 2 illustrates prognosis in a simple form: "When sleep puts an end to delirium, it is a good sign"; also, II. 16: "When in a state of hunger, one ought not to undertake labor", and II. 48: "In every movement of the body whenever one begins to feel fatigue, it will be relieved by rest", and II. 4: "Neither repletion, nor fasting, nor anything else, is good when more than natural". II. 21 has an appeal in these days of depression and secret ballots on Prohibition, "Drinking strong wines cures hunger", and II. 11 belongs to it: "It is easier to fill up with drink than with food". A good example of thoughtful medical observation is reflected in I. 14: "Growing bodies have the most innate heat; they therefore require the most food, for otherwise their bodies are wasted. In old persons the heat is feeble, and therefor they require little fuel, as it were, to the flame, for it would be extinguished by much. On this account, also, fevers in old persons are not equally acute, because their bodies are cold". There are many aphorisms on diet. I. 4 reads: "A slender and restricted diet is always dangerous in chronic diseases, and also in acute diseases, where it is not requisite". And again, "A diet brought to the extreme point of attenuation is dangerous; and repletion, when in the extreme, is also dangerous". II. 38 shows a diplomatic method still useful in practical dietetics: "An article of food or drink which is slightly worse, but more palatable, is to be preferred to such as are better but less palatable".

Therapeutic directions are numerous and varied. II. 37 reads: "Purgative medicines agree ill with persons in good health". Hellebore, which many of us have never had occasion to prescribe, played an important part in ancient Greek medicine. We find it in IV. 16: "Hellebore is dangerous to persons whose besh is sound, for it induces convulsions", and V. 1, "a spasm from taking hellebore is of a fatal nature", but IV. 15: "When you wish the hellebore to act more, move the body, and when to stop, let the patient get sleep and rest".

Bleeding, of course, was much in use, and the advice in VI. 47: "Persons who are benefitted by venesection or purging, should be bled or purged in spring", was widely observed until late in the last century. The same advice, without the purging, was repeated in VII. 53. The rules about purging are extensive. IV. 5 says: "About the time of the dog-days, and before it, the administration of purgatives is unsuitable". Adams tells us

that this rule was followed by all the Greek and Arab physicians. According to Galen, it is fighting against nature to determine inwardly by purgative medicine, while the heat is determining outwardly. Even now I think we are not agreed upon the advice in I. 24: "Use purgative medicines sparingly in acute diseases and at the commencement, and not without circumspection".

Aphorisms dealing with surgical problems are numerous and interesting, but I shall give only a few. VI. 6: "A severe wound of the bladder, of the brain, of the heart, of the diaphragm, of the small intestines, of the stomach, and of the liver, is deadly". Galen points out that the word "deadly" is often used in the sense of "very dangerous". VII. 14 says that "stupor or delirium from a blow on the head is bad". VI. 8: "In dropsical persons, ulcers forming on the body are not easily healed". VI. 38: "It is better not to apply any treatment in cases of occult cancer (meaning either not ulcerated or deep-seated); for if treated the patients die quickly; but if not treated, they hold out a long time". IV. 79: "In those cases where there is a sandy sediment in the urine, there is calculus in the bladder or kidneys". Galen added the words "or kidneys", saying they were not mentioned in the copies of the Aphorisms then in use. A belief still encountered is shown in VI. 12: "When a person has been cured of chronic hemorrhoids, unless one be left, there is danger of dropsy or phthisis supervening".

Gynecology and obstetrics are freely represented. V. 50: "If you wish to stop the menses in a woman, apply as large a cupping instrument as possible to the breasts". V. 42: "A woman with child, if it be a male, has a good color, but if a female, she has a bad color", raises many questions about the accuracy of observation, while V. 38 clearly goes back to the very old belief in the uterus as a two-chambered organ; it reads: "If, in a woman pregnant with twins, either of her breasts lose its fulness, she will part with one of her children; and if it is the right breast which becomes slender, it will be the male child, or if the left, the female". By the time of Galen the error had been recognized. V. 49 is interesting ethnologically, because Adams tells us the practice was popular in the North of Scotland in his time, about one hundred years ago. The Aphorism says: "To procure the expulsion of the secundines, apply a sternutatory, and shut the nostrils and mouth".

The First Aphorism is in two sentences, which I shall consider in the reverse order, for the second sentence forms a fitting introduction to the technical aphorisms that follow. It reads, in Adams' translation: "The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants, and externals cooperate." This reveals a wise and experienced physician who knew well one of the most important parts of the practice of his art. He knew the votary of the Old Medicine, who had left his crutch and his votive offering in the Esculapian temple; he knew the solicitous relatives, from grandmother down, the fussy neighbors, with recommendations from the market place, the theater and gym-

nasium, and the advocates of all the cults, and he avoided all discussion and argument in one apodictic sentence. The beginning of the Aphorism is also, I think, best rendered in English by Adams, as follows: "Life is short, and the Art long; the occasion fleeting; experience fallacious, and judgment difficult". The opening words have arrested the attention of some of the most acute minds in all the ages. Cicero, Horace, Seneca, Pliny the Elder, Juvenal, Martial, Sallust, and other Roman writers knew them. Moliére used the first part of the aphorism in a medical comedy, "The Flying Doctor". Goethe quoted "Life is short, Art long" twice in the First Part of "Faust". Longfellow's use of the words in the "Psalm of Life" is well known. Daremberg, the learned medical historian said: "The beginning of the Aphorisms has an incomparable majesty. It is impossible to imagine expressions so brief and so striking for describing the grandeur of Medicine and the responsibility of the physician". In the original Greek the Aphorism is even more concise than is most translations, as the Greeks omitted verbs, so that we might read: "Life short, but the art long", etc. It is an interesting proof of the practical value of the Greek language that of the ten chief words in the first half of the Aphorism, seven are in daily use in English words like biology, brachycephalic, technic, macrocosm, empiricism, oxygen, and crisis, and two others are used in chemistry. It is hardly necessary to say that all medical commentators hold that "Art" means the Art of Medicine. The context makes this clear, but no medical man can object to the more general application, as by Goethe and Longfellow.

The next phrase, "Occasion fleeting" deserves comment. The word used for occasion means not time in a general way, but "fit", "proper", "exact or critical time"; "time in reference to subject". It corresponds to the Latin "opportunitas". The word for "fleeting" is literally "sharp," "pointed", "cutting", "vehement", "prompt", "fleeting".

It is easy to see from this alone the keen therapeutic sense of the author. We can understand how it was that he seized the time for opening an empyema, and we can imagine how his mind would have appreciated the exigent medicine of today, with a perforated peptic ulcer, an acute appendicitis or an empyema of the gall-bladder, a twisted pedicle, a tumor of the spine, or a meningitis. Yet the needed promptness runs a risk, at present, of being missed by reason of the technical details that seem necessary and that can be done more rapidly if promptness is realized as essential. I often think how applicable a certain saying attributed to Napoleon is in such cases. It is said that after an early Italian battle the opposing commander asked for an armistice in order to improve his position. Napoleon, with more oratory than Grant on a similar occasion, said "No", adding: "It may happen that I shall lose battles, but you will never catch me losing minutes, either by overconfidence or sloth." In converting Greek into medieval Latin there were some difficulties. "Occasio" that is, "opportunity", "fit time", or "favorable time", is nearly always used by early editors, but "tempus"

was used by Hugo of Siena (d. 1439) in a Venice, 1498, edition (Osler Library, No. 171), and in the Florence Articella of 1534. It also appears in the Van der Linden edition, Lugd. Batav., 1665. "Acutum" was used for the 1498 and 1534, "praeceps" for the 1665. Praeceps, "headlong", "sudden", was the adjective most frequently following "occasio", but "celeris", and "volucris", "fleet", are also used. Heurnius, 1543-1601, who edited many editions, was not satisfied with such simple language and said "Occasio momentosa & magni momenti". A few editors introduced a "nevertheless" into the phrase. English, French and German editors followed the general ideas, and we find "occasion sudden", "l'occasion echappe" (Le Clerc, 1702), "l'occasion passe vite", "l'occasion prompt a echapper", "l'occasion fugitive"; and "rechte Augenblick", "Gelegenheit flüchtig", "schnell vorübergehend", "plötzlich". Dr. Eliot used "occasion instant" in the inscription for one of the Harvard Medical School buildings, an unusual word equivalent to "urgent". (See Second Epistle of Paul to Timothy, Rev. vers. 4, 2: "be instant in season, out of season".)

The next clause, "experience fallacious", has caused more difficulty to translators than any other part, and furnishes an interesting study. "Experientia fallax" is a frequent Latin form, and can be traced back to soon after 1500, but "experimentum fallax" seems older, i.e., 1498 (Hugo de Siena). While we now distinguish easily between "experiment" and "experience", that was not always so. Both words came from "Peira", and when we test this word by its early use, we find that it indicates such things as trial, attempt, undertaking, thing to be proved, and so makes the basis of the old and modern word empiricism. It often included attempts the outcome of which might be uncertain. So it was used for a trick, a stratagem, hence a robbery or piracy; a temptation, in ecclasiastical writing; an attempt to seduce a female, an action by sea, and so on. The qualifying adjective, translated "fallacious", means more frequently "slippery", or "likely to cause a slip, fall or hurt; insecure; doubtful, delusive; perilous, reeling, unstable".

Galen recognized the point of weakness in the phrase, and commented at considerable length, but also with some obscurity. It seems clear that he meant that therapeutic experiment is dangerous, because it may involve the life of a human being. But we must understand the position of therapeutics at the time, with its division into sects, the Methodists who relied upon theory, the Empirics, who tried experiments, and the Dogmatists, who took a middle course. Evidently the Hippocrates who objected to the routine use of hellebore was not the same who incised the empyema. In the former case he was probably right in withholding the drug, but in the latter he was trying the 'dangerous experiment" of operation rather than leaving the patient to die according to rule. If the incision did not heal, and the patient had what we now recognize as a tuberculous empyema, Hippocrates might well have said "experience fallacious". Then as now, different degrees of faith in rules affected one's

practice. Guy of Chauliac with Gallic keenness read that part of the aphorism, "experience fallacious and dangerous". As printing went on "experimentum periculosum" was preferred, and "experimentum fallax" rare, and "experientia periculosa" almost disappeared, reviving in 1829, while "experientia fallax" disappeared and reappeared in a similar way. In the Foës-Plant edition of 1633 (Lugd.) Foës preferred "experientia fallax", while Plant chose "experientia periculosa". Heurn, who had to make matters more emphatic, introduced "empirica periclitatio periculosa" (1601, 1609, 1627, 1633). Even before the experimental age was conscious of its surroundings, the question of interpretation had to be considered, and so we find Paracelsus making a characteristic pronouncement. For a copy of this I have to thank Dr. W. W. Francis. It is taken from No. 177 of the Osler Catalog. Except for Paracelsus specialists it would be too long to quote in full. Paracelsus states that "in the beginning" there was no Theory, but only Experience: "this loosens, that constipates". "Scientia ... ist nimmer Experimentum fallax: das macht die Theorika medica, etc".

Dr. Francis has also found an interesting comment in the "Medicina Hippocratica exponens Aphorismos Hippocratis". Auctore Johanne de Gorter. Ed. Prima Italica. Patavii, 1747. From this it seems that de Gorter distinguished between experiment and experience, and went on to say: "Not every experiment is perilous, for many physicists and chemists have made many experiments, in which there was no peril. But in medicine an experiment is perilous, for the end of a rash experiment is death". Modern languages, of course, give only a reflection of the perplexities of the earlier Latin writers. So we see that in Le Clerc in 1702, Dezeimeris in 1841, and Littre in 1845 "trompeuse" is used to describe "l'experience"; Daremberg put it: "l'empirisme est dangereuse". The Germans began later, and followed the same lines: J. F. C. Grim, 1837: "Erfahrung trügerich"; Fuchs, 1895: "Versuch trügerich"; Kurt Sprengel, 1789: "Erfahrung misslich"; J. A. Petschaft, 1825: "Der Versuch gefährlich".

The English translation of Sprengel of 1708 is very crude and puts the phrase: "to make experiments dangerous". An early English edition, anonymous, the Preface signed "S. H." London, 1610 puts it: "experience uncertain". It was a refreshing variation when Francis G. Benedict took President Eliot's version and made "experiment" an experiment in the modern way, not a therapeutic essay perhaps hundreds of years old, but a formal, scientific procedure; gave a brilliant plea for the Aphorism as a guide: "where the occasion for observation, for test or proving may exist but for a short time ... and the danger of not making the critical experiment at the proper time is indeed perilous". The recent discussion on "The Art and Human Nature" by Stewart R. Roberts* gives eloquent testimony to the vitality of the aphorism as a guide to the Art in its clinical application.

*Roberts, Stewart R.: The Art and human nature, New Eng. Jr. Med., 1932, ccvi, 70-76.

The last clause in the sentence, "judgment difficult", has come down in almost the same words in all the versions I have examined, "judicium difficile" (Lat.), "jugement difficile" (Fr.), "urtheilen schwierig" (Germ.). This is all the more remarkable since a simpler and more clinical meaning was near at hand. For the word "krisis", translated as "judgment" or "decision", involving choice or discrimination, also was used by Hippocrates for the crisis or critical stage of an illness. I find myself rejecting the latter interpretation "the crisis of a distemper", difficult, and agree with the more metaphysical interpretation given by so many others who have been puzzled and fascinated by the old but immortal medical theme "Life short, but the Art long, opportunity fleeting, experience fallacious, judgment difficult".

A Neglected Research

"MY SUGGESTION on this occasion [is] to initiate a thorough study of the problem of longevity in its special application to the medical profession. I feel strongly that a study of the lives, the habits and the recreations of, say, one thousand men of mark in the medical world for the last quarter of a century would make an extremely valuable contribution to knowledge. And this study should be amplified by research into all the more promising studies thus far made into the cause of death in the medical profession in this and other countries, with due regard to ages at death and the lessons to be learned from the countless instances of premature demise. Let guesswork and crude speculation be replaced by an authentic study of the salient facts, for it goes without saying that the nation suffers no greater social losses than that of the wasted years of life in the part of its medical men who die many years in advance of their attainable time.

"No career presents more strenuous mental effort, more exacting demands upon time, more sacrifice of means, more foregone leisure, than that of the doctor who takes his work seriously, and there are few who do not. No class of men renders a greater and more indispensable service to society than those who practice the art of medicine, in all its branches and selected specialists. Upon no group of men falls a heavier burden or a greater responsibility in peace and in war. And none has done more to advance the cause of a true civilization, in which the blessing of a long life and freedom from illness and suffering is made the supreme test of its attainment on the part of an ever-increasing proportion of mankind. Yet, as I have shown, the evidence regarding its own health and longevity is decidedly disconcerting, while suggestive of neglect that justifies the inquiry suggested." FREDERICK L. HOFFMAN, LL.D., in *Life and Death in the Medical Profession*, 1932, The Prudential Insurance Company of America, Newark, New Jersey.

Editorial

NON-MEDICAL DISTRIBUTION OF DRUGS AND MEDICINES

The social, medical, and economic importance of the distribution and employment of drugs under other than proper medical direction is forcefully set forth in a recent publication* from The Committee on the Costs of Medical Care. In this report it is stated that the people of the United States spend each year approximately $715,000,000 for drugs and medicines, of which only 27 per cent ($190,000,000) is the portion expended for prescriptions, or for other purchases made with the direct advice of medical practitioners. This means that the public spends annually $525,000,000 for self-medication in its various forms. The retail sales of home remedies account for $165,000,000. These are usually bought without the express instruction of the medical profession, but may have been purchased at the suggestion and oftentimes with the approval of medical practitioners. The nation's bill for "patent medicines" comes to $360,000,000. In the words of the Abstract of this publication (Number 14):

"Thus a total of $525,000,000 is spent by the American people for medicines on their own initiative to cure minor or chronic ills which seem too trivial or too frequent in occurrence to warrant a call upon a medical practitioner, and to alleviate temporarily physical or mental symptoms which may or may not be the danger signals of serious disorders." The total amount spent for drugs and medicine is roughly of the same general order of magnitude as the sum spent for the services of physicians, or for hospitalization, and represents a charge, on the average, of between $20 and $25 per family per year. Since such purchases are made voluntarily by people who still have their earning capacity, and are distributed throughout the year, they have not been considered a burden and have not provoked unfriendly or critical discussion.

The "drug stores" of this country receive each year $485,000,000 from the sale of home remedies and "patent medicines". The remainder of the expenditure for self-medication goes to mail-order houses, general stores, herbalists, itinerant vendors, etc. Aspirin, and sometimes more potent anodynes and soporifics, can be obtained in many restaurants and at soda fountains not connected with drug stores. One must have a good deal of sympathy for the pharmacist in the position in which he finds himself. If he conducts his business with conscientious regard to the ethical code of his profession, which decrees that he must not assume the functions and prerogatives of a physi-

*The Costs of Medicines; The Manufacture and Distribution of Drugs and Medicines in the United States and the Services of Pharmacy in Medical Care, by C. RUFUS ROREM, Ph.D., C.P.A., and ROBERT P. FISCHELIS, B.S., Phar. D., University of Chicago Press, 268 pages, April, 1932. Price in cloth, $2.50. Abstract obtainable from The Committee on the Costs of Medical Care, 910 Seventeenth St., N.W., Washington, D.C.

cian by attempting to diagnose a customer's condition or by prescribing medicines for him, he does so in full knowledge that he is playing to the hand of a less conscientious competitor. At a time when the standards of education and experience which must be met in order to qualify for licensure as a pharmacist are being raised in many states, the whole tendency of pharmacology, therapeutics and pharmaceutical manufacture is such as to give the pharmacist less and less opportunity to practice the science of compounding medicines. He is forced to turn to merchandising, to catering, and to the art of salesmanship in order to secure economic independence. Although fewer doctors compound and dispense remedies from their offices, there is an increasing tendency for physicians to prescribe medicines already compounded under proprietary names. Judging by the advertisements which crowd many European medical journals, this tendency has reached a level on the continent which we may earnestly hope will never be approached here.

While the better type of druggist no longer stocks patent medicines for venereal diseases and deprecates over-the-counter prescribing for them, it is common knowledge that it is in connection with this group of diseases that the most flagrant disregard for professional ethics and public welfare exists. That which is 'common knowledge' is likewise supported by thoroughly controlled investigation. In the course of a survey* of the medical aspects of social hygiene in San Francisco, questionnaires were filled in and returned by 130 drug stores. Of these, 79 per cent reported that 1,545 patients with disorders thought to be gonorrhea and 323 with disorders thought to be syphilis had applied for advice or for remedies during the month of July, 1931. Of the 102 druggists who stated what they did for those requesting such aid, 19 per cent admitted that they furnished remedies; 10 per cent furnished remedies occasionally, but in some instances referred them to a physician or clinic; 49 per cent always referred inquirers to a physician or clinic; and 23 per cent stated that they gave no information. As a check on the answers given, investigators visited 120 such establishments and gave a vague account of symptoms leading to an inference of the presence of venereal disease. The replies received indicated that 56 per cent of the drug stores visited were willing to undertake the illegal practice of medicine by diagnosing, or by prescribing, or both. Only 31 per cent definitely refused either to diagnose or to prescribe, and advised the inquirer to go to a doctor or clinic. Similar investigations have been conducted in several other cities. In Chicago, 63 per cent of the drug stores visited made diagnoses and offered to sell remedies or to treat syphilis or gonorrhea; in New Orleans, 34 per cent; in Washington, D. C., only four per cent. In addition, 445 young men of San Francisco were interviewed casually on the street and in barber shops and pool rooms to ascertain what they would do, or advise doing, if infected with a venereal disease. Thirty-six per cent advised going to a drug store

*Walter F. Snow, M.D., and Walter Clarke, M.D.: Medical aspects of social hygiene in San Francisco, Jr. Social Hyg., 1932, xviii, 245-276.

for aid, as compared to 23 per cent who would go to a physician and 18 per cent who would go to a clinic. There were six per cent who advised going to an herbalist or similar charlatan.

The extent to which the Chinese herb doctor, whose materia medica includes weird "remedies" of animal as well as vegetable origin, flourishes along the Pacific slope is almost beyond belief. The survey to which reference has been made revealed over 75 Chinese herb shops in San Francisco and vicinity alone. It is estimated that there are more than a thousand of them in this country. During the survey 12 herbalists were visited and all offered to sell remedies to "cure" syphilis or gonorrhea. "Six out of eight herbalists to whom letters were written diagnosed one of these diseases by means of the insufficient symptoms described in the letters and 'guaranteed' to cure by correspondence. The terms ranged from $10 to $50."

In the current telephone directory of one of the larger cities of the state of Washington there is displayed an advertisement which reads, in part, as follows: "Wing Wo Chinese Medicine Co., established 1899. Come in no matter what your ailment. The Chinese successfully use roots, herbs, barks, and berries for every ailment of mankind." Whether such concerns can be prosecuted under medical practice acts or not, it is extremely unlikely that the telephone company would in this instance continue such advertising if proper representations were made to it by the County and State Medical Societies.

There are a number of ways in which the practitioner can do something to lessen this distribution of drugs without proper medical supervision. Here his personal interests are in such full accord with those of public welfare that he need not feel hampered lest his activities be construed as entirely self-serving. He should lose no opportunity to keep before his clientele and the lay public the fact, so much to their advantage, that the indispositions for which they undertake self-medication may be the manifestations of serious affections which require diagnosis in their early stages if they are to be cured or controlled. He should invoke the aid of, and lend his support to, those possessed of legal authority, as well as better business bureaus, and other agencies to secure the elimination of those practicing medicine illegally, or making fraudulent promises of cure. Finally, he should secure, in so far as possible, the sincere cooperation of pharmacists. He can demonstrate his appreciation of the problem facing the pharmacist by refraining from being a competitive compounder of medicines himself, and by prescribing in such a manner as to make use of the professional knowledge and skill of the pharmacist, rather than depending largely upon medicines already compounded and sold under proprietary names. Both economically and therapeutically the patient should benefit by such a course of action.

Abstracts

Death Rates in a Group of Insured Persons. (Public Health Reports, 1932, xlvii, 437-440.)

Tables which can be found in the Statistical Bulletin of January, 1932, issued by the Metropolitan Life Insurance Company, provide an index, in advance of governmental figures, of the mortality status of the general population. They present the mortality experience of the industrial department of this company, by principal causes of death, for 1931 as compared with 1911 and 1921-1930, inclusive, and for December, 1931. The rates for recent years are based on between 17,000,000 and 19,000,000 insured persons in the United States and Canada. Although this is a more or less selected group and is largely urban, the death rate is a fair indication of the trend in the general population. In recent years the general death rates in this group have been averaging about 72 per cent of the death rate for the registration area of the United States. Six diseases, tuberculosis, diphtheria, whooping cough, pneumonia, diarrheal complaints, and puerperal conditions, recorded lower mortality rates in 1931 than ever before. The rate for typhoid fever equaled the minimal figure previously attained. The mortality rate for tuberculosis dropped 5.7 per cent in spite of the prevailing economic conditions. This is a larger decrease than the average year-to-year decline during the preceding decade; and the rate is 65.9 per cent lower than for 1911. Mortality from diphtheria showed a drop of 24.6 per cent in one year and of 50 per cent in two years. In spite of an incipient epidemic of influenza at its beginning, the year ended with a new minimum for the death rate from pneumonia. The death rate for diseases of pregnancy and childbirth showed a reduction of 3.3 per cent for this group as compared with 1930. Part of this decline is apparent only, being due to the falling birth rate. That some of the reduction is real can be demonstrated by computing the rate on the basis of live births. New minimal death rates were recorded for accidental burns and for injuries in railroad accidents, and rates lower than those in 1930 for alcoholism and chronic nephritis. On the other hand, an increase of 7.4 per cent appeared in the death rate for cancer in 1931. While the death rate for diseases of the heart is slowly rising, the increase is found in the older ages only. Diabetes recorded a new high rate, 14.4 per cent greater than in 1930 and 61 per cent above that of 20 years ago. Here the increase is in the age group past 45 years, and particularly among women. The mortality from automobile accidents increased more than five per cent over the rate for 1930. For this cause of death there has been a rise of almost 900 per cent in 20 years, and it is estimated that not less than 34,000 people lost their lives in automobile accidents in the United States in 1931. The Bulletin upon which this article is based states that "as yet there has not been any appreciable injury to the public health from the economic conditions that have prevailed".

[Editorial Comment: As has been pointed out previously in the editorial columns of the ANNALS, the reasons why present economic conditions have not produced a recognizable deleterious effect in respect to mortality and morbidity are multiple. Even in economic depression itself there are positive and negative public health factors, the algebraic sum of which is not easily determinable. After all, study of such statistical analyses as that of the paper here abstracted, leaves the firm impression that the chief factor in lowering mortality rates has been the progress which Medicine has made in the prevention and treatment of those diseases which take their heavy toll before the middle period of life. Rising mortality rates for the so-called degenerative dis-

eases must be expected, since all must die. Life-savings at one end of the scale must be balanced by life-losses at the other, for preventive medicine can neither bestow immortality nor appreciably alter the histogenetic life limit imposed upon human protoplasm by the evolutionary processes of millions of years. Rather may we not expect that the proportion of those past middle life who will attain extreme old age will decrease, since there will be preserved to reach that group some who are intrinsically less resistant? One must view with apprehension the rapidly rising list of automobile casualties, preventable for the greater part, and yet taking an annual toll from all walks of life, including those best fitted to render significant service to the race. Our own profession pays a heavy tribute to this cause of death.]

Cirrhosis of the Liver. By FRANK B. MALLORY, M.D. (New Engl. Jr. Med., 1932, ccvi, 1231-1239.)

Among 9346 autopsies performed at the Boston City Hospital during the past 35 years there were found 550 examples of well-marked hepatic cirrhosis, an incidence of 5.88 per cent. These were classified as follows:

Alcoholic cirrhosis ...	270	48.90 per cent
Pigment cirrhosis ..	49	8.90 per cent
Healed acute yellow atrophy	46	8.36 per cent
Syphilitic cirrhosis ..	28	5.09 per cent
Colon bacillus cirrhosis	25	4.54 per cent
Obstructive cirrhosis	24	4.36 per cent
Obstructive and colon bacillus cirrhosis .	3	0.54 per cent
Cancer cirrhosis	1	0.18 per cent
Not classified	104	18.90 per cent

It was found that healed acute yellow atrophy and syphilitic cirrhosis may occur at any age, but alcoholic cirrhosis and pigment cirrhosis are practically limited to adult life, and cause death at a late age, indicating that these latter lesions require many years for development. The incidences of ascites, jaundice, esophageal varix, hemorrhage and of various degrees of enlargement of the spleen are given for each type of cirrhosis represented in the series. Enlargement of the spleen with increase in stroma elements was of frequent occurrence and is directly due to the obstruction to the flow of portal blood through the liver. Twelve examples of primary liver cell cancer were encountered. Four of these were in association with pigment cirrhosis and three each with alcoholic cirrhosis and healed acute yellow atrophy. Obstructive cirrhosis is caused by occlusion of either the hepatic or common bile duct. There results a slight to considerable sclerosis around all of the bile ducts, producing a smooth to finely granular cirrhosis which is commonly called biliary cirrhosis. The cirrhosis produced by an ascending colon bacillus cholangitis likewise involves the bile ducts and the immediately surrounding tissues. If any type of cirrhosis should be recognized as Hanot's, it would seem to be the early stage of this. [The editor has thought that diffuse congenital syphilis in an adult liver more nearly meets the conception of Hanot's cirrhosis.] It seems probable that in addition to the well-known group of toxic substances, capable of producing acute yellow atrophy of the liver, the direct action of a streptococcus must be added in considering the etiology of this important form, which is so frequently missed in clinical diagnosis. Pigment cirrhosis forms the first and most important lesion in hemochromatosis. It is characterized by the presence of two pigments in the liver cells, hemofuscin derived from hemoglobin and hemosiderin which is slowly developed from the hemofuscin. Pigment cirrhosis can be produced in rabbits, sheep and monkeys by means of chronic copper poisoning in 6 to 12 months provided the dose is large enough. In man, as far as can be ascertained from clinical observations, well-marked pigment cirrhosis requires in the neighborhood of fifteen years for development. The chief sources of chronic copper poisoning are to be found in the copper coils used in distilling apparatus; in wines made from grapes upon which copper containing insecticides have been sprayed; and in occupations involving the cutting, grinding, and polishing of copper and brass. As to alcoholic cirrhosis, all experimental evidence is against alcohol itself

being the cause of this lesion. The essential histopathological lesion, hitherto not generally recognized, involves the development of minute hyaline droplets within the cytoplasm of the liver cells. These droplets fuse to form an irregular hyaline meshwork about the nuclei. There is some experimental evidence that a similar basic lesion is produced by phosphorus, so that the suggestion is made that this substance may be the cause of so-called alcoholic cirrhosis. However, the presence of phosphorus in alcoholic beverages has not been demonstrated as yet so that certain desirable links in the chain of evidence are still missing.

Auricular Fibrillation: Ambulatory Treatment with Quinidine. By S. A. Weisman, M.D. (Arch. Int. Med., 1932, xlix, 728-734.

This article deals with 24 patients with auricular fibrillation who were treated by the ambulatory method with quinidine sulphate in the outpatient department of the University of Minnesota. All patients were first given digitalis. If the heart is decompensated the patient is well digitalized until there is evidence that the heart is fully compensated, or nearly so. Quinidine is then given in small doses: 0.1 gm. on the first day; 0.2 gm. on the following day, and on the third day, 0.4 gm. For five days this dose is maintained, with 0.1 gm. taken every two hours. At this point the digitalis may be reduced or discontinued. On the seventh day the dose of quinidine is increased to 1 gm. per day (5 grains every two hours until three doses have been taken). Later the amount may be increased to 20, 30, or even 40 grains per day, always given in divided doses at two hour intervals. As soon as cardiac rhythm becomes regular the dose of quinidine is reduced, and a maintenance dose is established. This may be 5 grains daily, or 5 grains every other day. Normal rhythm was restored in 17 of the 24 cases treated, that is, 70.8 per cent. Eighteen of the 24 patients were 50 years of age or over; in 14 of this group, 77 per cent, the heart was restored to normal rhythm. Regular rhythm was restored, also, in three of the remaining six. Those with hypertension seemed to respond more quickly than the rheumatic group. Two accidents occurred during treatment: one death from coronary thrombosis, and one case of hemiplegia.

A Case of Friedländer's Pneumonia. By E. H. Bensley, B.A., M.D. (Canad. Med. Assoc. Jr., 1932, xxvi, 681-684.)

The patient, an adult, white male, 42 years of age, was well until three days before admission to the Montreal General Hospital. On rising in the morning, he had vomited, soon suffered from headache, and had chills, warm flushes and sweats, cough, and expectoration. The temperature ranged between 101.4° and 104.4°, and signs of consolidation appeared at the left base on the day following admission. The patient's condition became steadily worse and he died 38 hours after admission to the hospital, on the sixth day of the illness. At autopsy, the entire upper lobe of the right lung and large portions of both lobes of the left showed consolidation. From the cut surface of the solid areas, a large amount of mucinous greyish purulent material was exuded. Microscopical examination showed considerable numbers of large mononuclear cells as well as polymorphonuclear leucocytes in the alveoli. Red cells and fibrin were less prominent in the exudate than is usually true of pneumococcal pneumonia. The Friedländer's bacillus was obtained from three sources in this case—the sputum (ante mortem), ante mortem blood culture, and post mortem blood culture. A white mouse, inoculated intraperitoneally with washed sputum, yielded pure cultures of Friedländer's bacillus from the heart's blood and the peritoneal exudate.

Reviews

Cancer: What Everyone Should Know About It. By JAMES A. TOBEY, Dr. P. H., Fellow, American Public Health Association; Associate Fellow, American Medical Association; Member, American Society for the Control of Cancer. With introductions by JOSEPH COLT BLOODGOOD, M.D. and H. L. MENCKEN. 323 pages with 17 illustrations. Alfred A. Knopf, New York, 1932. Price, $3.00.

Cancer, What Everyone Should Know About It, is written, as the title indicates, particularly to inform the laity about cancer. The author has taken pains to explain all medical terms and procedures in detail. Dr. Tobey describes the nature of cancer and gives its history throughout the ages. A chapter is devoted to brief life stories of famous persons who had cancer, as the Bonaparte family, Presidents Grant and Cleveland, and many others. In giving the types and locations of cancer it is stated that cancer of the stomach is the most serious form of the disease, causing about one-third of all deaths from cancer. He believes it to be as curable as any other form when an early diagnosis is made. More frequent gastrointestinal X-ray examinations are advocated in all cases of chronic dyspepsia in the hope of reducing the mortality of cancer of the stomach.

"Danger signals of all cancers can be summarized in these words:

1. Any lump in the breast or other part of the body, especially one which begins to grow or change;

2. Any sore that does not heal, particularly on the face or mouth;

3. Any unusual discharge or bleeding from any part of the body. Pain, it should be remembered, is always one of the later symptoms."

In regard to treatment:

"No member of any of the healing cults outside the pale of regular medicine is capable of giving proper treatment for cancer, and faith healing is worse than nothing." He emphasizes that there is no serum nor vaccine, no salve, plaster or paste and no chemical, except radium, which had been proven to alleviate cancer. In regard to irradiation, x-ray or radium, he states that "it cannot surpass surgery in many instances, and in others it is only a supplement to it, but in numerous cases it is an effective substitute. He gives an interesting review of the history of x-ray and radium, particularly Madame Curie's life and work. Dr. James Ewing is quoted as to the heredity of cancer, whose view, in brief, is that the hereditary influence does not convey the disease but only structural peculiarities rendering certain organs especially prone to cancer. Dr. Maude Slye's work and Dr. Warthin's cancer family are also described. The author makes it clear that contagion plays no part in the causation of cancer and repeatedly warns against quack cancer cures, telling at length of the evils of "The Great American Fraud". He advocates surgery, x-ray and radium as the only known treatment of cancer. The whole message is one of hope and cheerfulness. The author feels that cancer is largely preventable with proper knowledge, and curable if diagnosed and treated early. But how very often it is impossible to make an early diagnosis, because of inaccessibility and lack of definite findings! But to err in the direction of optimism may not be altogether a fault in a work intended for intelligent laymen.

R.C.W.

Applied Pharmacology. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S.; Professor of Materia Medica and Pharmacology in the University of Edinburgh; formerly Professor of Pharmacology in the University of Cape Town, and later in the University of London. Fourth edition,

590 pages, 72 illustrations. P. Blakiston's Son and Co., Inc., Philadelphia, 1932. Price, $4.00 net.

This edition of Applied Pharmacology follows its predecessor after an interval of but two years. This has been necessary in order to incorporate the recent advances in therapeutics. This book differs from the purely academic presentation of Pharmacology in an effort to bridge the gap which is too often widely existent between that science and therapeutics. Thus we find the subject matter arranged, for the greater part, according to organs and systems with a view to function, rather than with regard to the origin or nature of the medicinal agents themselves. Throughout, the aim has been to present such actions of drugs as are capable of scientific demonstration. There are certain minor changes which, in the next edition, would increase the usefulness of this book. Some point is made of the relative costs of drugs, but these values are in English currency requiring the American reader to transpose to terms with which he is more familiar. It is questionable whether a chapter of but 17 pages covering all forms of radiations is worth including or even germane to the subject covered by the title. Although familiar with the work of Aub and his associates, the author seems to have missed the point (page 538) that the most effective treatment of some forms of lead poisoning is to promote lead fixation, as contrasted with lead elimination. The index has not kept up with the revision. Although the text includes a paragraph on ephedrine, the index does not refer to that drug. Aside from such minor faults, this is a very useful book, well-printed and unusually free from typographical errors.

United States Army X-Ray Manual. Second Edition, Rewritten and Edited by Lt. Col. H. C. Pillsbury, M.C., U.S.A. 500 pages, 228 ills. Paul B. Hoeber, Inc., New York City, 1932. Price in flexible leatherette, $5.00.

The first edition of this book was the joint product of several men and was intended to cover particularly the problems of war service. It was produced during the World War. Since then conditions have changed until the care of the sick of a peace time army and the service to World War veterans have given to the radiologists of the Army precisely the same problems as confront their colleagues in civil life. The chapters treated are X-ray Physics; Dangers and Protection; Laboratory Experiments; Fluoroscopy; Technic; Field Unit; Localization; Bones and Joints; Sinuses; Mastoids and Brain; Teeth and Maxillae; Thoracic Viscera; Urinary Tract, and Gastrointestinal Tract. Therapy is not considered; but in a clear and concise form there is provided an adequate description and discussion of apparatus, technic, and interpretation. Practical suggestions for safeguarding the use of x-ray apparatus and for handling radioactive substances make a valuable section. The localization of missiles and other foreign bodies is treated very completely. The mechanical structure of this manual is pleasing and practical. In addition to its special use in military service, this book is admirably adapted to the needs of those whose situation is such that they are required to do occasional roentgenologic work without the elaborate equipment of laboratories devoted exclusively to this specialty. Is it not equally true of the roentgenologist outside of the Army that "he must remember, however, that his work is valuable only in so far as he assists the physician or surgeon in arriving at correct conclusions, and that this can be accomplished only by mutual cooperation"?

Pathology for Nurses. By Eugene C. Piette, M.D., Pathologist and Director of the Clinical Laboratories of the West Suburban Hospital, Oak Park, Illinois; Consulting Pathologist, Chicago State Hospital. 251 pages, 65 illustrations, some in color. F. A. Davis Company, Philadelphia, 1932. Price, $1.75.

As clearly stated in the preface, and as apparent from the text, this book is intended to provide instruction in the fundamentals of pathology, of necessity simply and briefly put; and to give detailed practical instructions for the intelligent handling of specimens required for the laboratory. In general the subject matter is fairly well chosen to meet these ends. A simply written intro-

ductory chapter explaining what is meant by normal and abnormal life, health and disease, would be of value. There are many statements in respect to detailed pathology which are open to question. Some may be the result of an unusual personal experience. It is not the experience of most pathologists, for instance, to find that "diaphragmatic hernia is not an uncommon developmental anomaly". Curiously, actinomycosis is said to be caused by a "*yeast-like* organism", and to be a condition "rarely occurring in this country". The chapter headings are extremely misleading, for leprosy and Hodgkin's disease are considered in the chapter headed Tuberculosis, and gonorrhea and chancroid under Syphilis. Illustrations of malignant melanoblastoma, both primary and secondary, occur in the chapter headed Benign Tumors. This book shows the results of careful proof reading and non-medical editorial supervision. The typography is excellent.

Modern General Anesthesia, A Practical Handbook. By JAMES G. POE, M.D., Lecturer on General Anesthesia in the Medical and Dental Departments of Baylor University; Anesthesiologist of Baylor University Hospital of Dallas; Consulting Anesthetist to the Shriners' Hospital for Crippled Children, and Parkland Hospital, Dallas, Texas, etc. Second Edition, Completely Revised and Enlarged. 231 pages, 12 illustrations and 2 charts. F. A. Davis Company, Philadelphia, 1932. Price $2.50.

In Modern General Anesthesia the author presents the subject matter in a very clear and concise manner which should make the book of great value to the student of anesthesia. At the beginning is a very complete chart (which should be redrawn for the next edition to eliminate the misspelled words) showing the zones of the third stage of ether or ether sequence anesthesia. At the end of each descriptive section is a brief, easily followed outline of the important material in the section. Throughout the book, Dr. Poe stresses important points, some of which the untrained are likely to overlook. He also emphasizes the importance of standard colors for gas tanks to prevent confusion and accidents, particularly in emergencies. The author believes that the danger of ignition during the administration of ethylene is practically the same as with ether and warns of the danger of static ignitions occurring when using ethylene or ether in fractional rebreathing since there is insufficient humidity from rebreathing to eliminate the possibility of static discharge. The same danger exists in giving ethylene intermittently for relief of labor pains. He feels that ethylene has a decided place in anesthesia. The author discusses intelligently the choice of an anesthetic and states that because of its strong likelihood of causing protoplasmic poisoning, chloroform should not be used as an anesthetic except in emergency. The nonvolatile anesthetics and local and spinal anesthesia are described in detail. "Since the advent of the use of the pleasant gaseous anesthetics, every patient should be induced into anesthetic sleep as comfortably as they go to sleep in their own bed at home, and a technic that does not admit of this accomplishment has no place in modern anesthetic practive." This quotation is characteristic of the attitude of the author toward his chosen field.

R.C.W.

Courts and Doctors. By LLOYD PAUL STRYKER. xxv + 236 pages. The Macmillan Co., New York, 1932. Price $2.00.

"Taking a leaf from the pages of preventive medicine, I have tried to explain the nature of a malpractice action, in the hope that an understanding of this malady may render those who understand it more immune to its dread ravages." Thus does the author state the purpose of the work which he has so well accomplished. For many years the general counsel for the Medical Society of the State of New York, he draws upon a rich practical experience for much of the material presented. Most of the treatises on the legal aspects of the practice of medicine neglect the phase of the subject emphasized here; that is, those events and policies which bring the physician into court as defendant or expert witness in an action for malpractice. An extended discussion in parts I and II of the patient-physician relationship with the legal responsibilities borne by each

leads to the development in part III of the elements of the action for malpractice with a careful elucidation of the necessary proofs to be established by the plaintiff and the possible lines of defense which may be undertaken by the defendant. Of equal value is the explanation of the most common errors committed by physicians which expose them to malpractice suits. The simple, straightforward advice herein contained can scarcely fail to be of value to those in all the branches of medicine. For those interested in the many cases quoted and cited as illustrative material, very complete and satisfactory indices are provided. This interesting and valuable book went to the fourth printing in five months. It deserves to be a medical "best seller". J.C.B.

The Principal Nervous Pathways: Neurological Charts and Schemes with Explanatory Notes. By ANDREW THEODORE RASMUSSEN, Ph.D., Professor of Neurology, Department of Anatomy, University of Minnesota, Medical School, Minneapolis, Minn. 73 pages, 28 figures. The Macmillan Company, New York City, 1932.

As the outgrowth of an extensive teaching experience Rasmussen has prepared this monograph to aid the student in acquiring usable knowledge of the more important nervous pathways in the central nervous system. It represents a correlation and fusion of structural information (morphology) with knowledge of function, and thus it builds a dynamic conception of the nervous system. The structural diagrams are supplemented by schematic outlines embodying much of the same information. A certain element of dogmatic presentation is necessary to bridge the gaps in this field. This is inevitable; and such changes as may be made desirable by additions to our knowledge can be incorporated in the subsequent editions which are sure to be required for such a well-conceived book. While intended for the student, both undergraduate and more advanced, this should prove a valuable aid to the practitioner and a reference source not to be despised by even the professional neurologist.

College News Notes

POST-CLINICAL TOUR

Immediately following the completion of the San Francisco Clinical Session, about 125 members of the College and their families left on a Post-Convention Tour, visiting the Yosemite Valley, Los Angeles and environs, and the Grand Canyon of Arizona.

From Sunday morning, April 10, to Tuesday noon, April 12, the group were entertained in Los Angeles by members of Southern California, under the leadership of Dr. Francis M. Pottenger, the incoming President, and Dr. Egerton L. Crispin, Governor for Southern California. Trips were arranged through Hollywood and Beverly Hills to the sea, with a visit to the beautiful Japanese home and gardens of Mr. Bernheimer, overlooking Santa Monica Bay and the Pacific Ocean. Dinner and a delightful program were given at the Uplifters' Club. Will Rogers was among the entertainers at the Club, and many members had the opportunity of meeting him personally and shaking his hand. A visit was also made to Pasadena and the California Institute of Technology where the Wind Tunnel of the Guggenheim School of Aeronautics and the Million Volt X-Ray Tube were demonstrated. Dr. Pottenger acted as host to the entire group for luncheon on the lawns of the Pottenger Sanatorium in the foothills of the Sierra Madre Mountains in Monrovia. Members were also taken to the Huntington Library at San Marino, where they saw the Gutenberg Bible and the Huntington Galleries, where hang many rare and noted paintings, including the "Blue Boy". The Mission San Gabriel, one

PART OF THE POST-CLINICAL SESSION GROUP ON THE LAWNS OF THE POTTENGER SANATORIUM, MONROVIA

of the oldest of the historic Spanish Missions of early California, was also visited.

Never before has such a delightful Post-Convention Tour been arranged, and the appreciation of one and all was expressed to every member of the College in Southern California, who so graciously assisted in the arrangements of the program.

William D. Stroud Elected Treasurer of the College

Following the sudden and untimely death of Dr. Elmer H. Funk, who was elected Treasurer of the American College of Physicians during the San Francisco Session in April, the Board of Regents have elected Dr. William D. Stroud, of Philadelphia, Treasurer, with duties to start at once.

Dr. Stroud is Associate Professor of Cardiology in the University of Pennsylvania Graduate School of Medicine, Physician-in-Chief of the Heart Clinic, Pennsylvania Hospital, a member of the staff of the Robinette Foundation of the University of Pennsylvania, Physician-in-Charge of the Children's Heart Hospital, and Cardiologist to the Bryn Mawr Hospital.

Arrangements for Montreal Session, 1933

The Seventeenth Annual Clinical Session of the American College of Physicians will be held in Montreal, Canada, February 6-10, 1933. The Board of Regents of the College, during the San Francisco Session, specified the month of February, in accordance with the original practice of the College to meet in midwinter when there would be no conflicts with the meetings of other national bodies or of state societies. The local Committee on Arrangements at Montreal, of which Dr. Jonathan C. Meakins is General Chairman, selected the week of February 6 as a time that would be most suitable to the local profession, a time when the weather would probably be most settled, a time at which the winter sports are at their height, and the week preceding the meeting of the Council on Medical Education at Chicago, to which a number of the members of the American College of Physicians must go. The personnel of the Montreal Committees is as follows:

General Chairman:
Jonathan C. Meakins

Committee on Arrangements:
J. C. Meakins, Chairman
C. F. Martin
E. P. Benoit
J. E. Dubé
R. H. M. Hardisty
A. T. Henderson
Joseph Kaufmann
D. S. Lewis
E. H. Mason
C. F. Moffatt
I. M. Rabinowitch
C. G. Sutherland
H. P. Wright

Committee on Clinics:
J. C. Meakins, Chairman
C. F. Moffatt
I. M. Rabinowitch
E. P. Benoit
J. E. Dubé
H. P. Wright
E. Dubé

Committee on Auditorium and Local Transportation:
Joseph Kaufmann, Chairman
R. H. M. Hardisty
E. H. Mason

Committee on Publicity:
C. G. Sutherland, E. P. Benoit — Joint Chairmen
(Additional appointments pending)

Committee on Convocation and Banquet:
C. F. Martin, E. de L. Harwood — Joint Chairmen
D. S. Lewis
J. E. Dubé
A. T. Henderson

Committee on Entertainment of Visiting Women:
Mrs. J. C. Meakins, Convenor
(Additional appointments pending)

President F. M. Pottenger appointed on May 3, 1932, the following Nominating Committee:

James H. Means, Boston, *Chairman*
Noble Wiley Jones, Portland
Ernest B. Bradley, Lexington

Edward J. G. Beardsley, Philadelphia
Charles F. Martin, Montreal

The above appointments are in accordance with the provision of the By-Laws, Article I, Section 3, which states that the President "shall appoint within one month after induction to office a Nominating Committee of five, composed of two members of the Board of Regents, two members of the Board of Governors, and one Fellow at large, whose duty it shall be to nominate candidates for the elective offices, Board of Regents, and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective States, Provinces or Districts which will be represented by the nominees, if elected. The list of nominees for President-Elect, and for the First, Second and Third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting. This does not preclude nominations made from the floor at the annual meeting itself."

Under the sponsorship of Dr. A. B. Brower (Fellow), Dayton, Ohio, Governor of the College for the State of Ohio, a meeting and luncheon of all Ohio members of the College was held during the Ohio State Medical Association's meeting at Dayton during the first week in May. Those present decided to hold a similar meeting annually at the time of the annual meeting of the Ohio State Medical Association in the future. Among those who attended the luncheon were thirty-three Fellows and thirteen Associates.

Dr. Adolph Sachs (Fellow), Omaha, Nebr., Governor of the College for the State of Nebraska, was elected President of the Nebraska State Medical Association at the annual meeting of that society during the week of May 23.

Dr. Homer Davis (Fellow), Genoa, Nebr., was elected a Vice President.

Cecil O. Lorio (Fellow), Baton Rouge, La., was the symposiarch and contributed a paper on "Childhood Type Tuberculosis" in a symposium on tuberculosis by the Staff of Our Lady of the Lake Sanitarium, Baton Rouge, March 23, 1932. Dr. Lester J. Williams (Fellow), Baton Rouge, read a paper also, his subject being "X-ray of Tuberculosis".

During the five days following the San Francisco Clinical Session, Dr. Linn J. Boyd (Fellow), New York City, addressed the Sophomore, Junior, and Senior classes at the University of California, was the guest speaker at Dr. Kerr's Staff Conference, and addressed the San Francisco County Medical Society.

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows:

Dr. Frederick R. Barnes (Fellow), Fall River, Mass.,—1 reprint;

Dr. Grafton T. Brown (Fellow), Washington, D. C.,—1 reprint;

Dr. Lewis W. Brown (Associate), Newark, N. J.,—1 reprint;

Dr. I. W. Held (Fellow), New York, N. Y.,—10 reprints;

Dr. Roland N. Klemmer (Fellow), Lancaster, Pa.,—2 reprints;

Dr. Lowell L. Lane (Associate), Philadelphia, Pa.,—3 reprints;

Dr. James Z. Naurison (Fellow), Springfield, Mass.,—1 reprint;

Dr. Paul H. Ringer (Fellow), Asheville, N. C.,—4 reprints;

Dr. Karl Rothschild (Fellow), New Brunswick, N. J.,—1 reprint;

Dr. W. E. R. Schottstaedt (Fellow), Fresno, Calif.,—1 reprint;

Dr. Leon L. Solomon (Associate), Louisville, Ky.,—2 reprints;

Dr. Henry K. Taylor (Fellow), New York, N. Y.,—1 reprint;

Dr. Edwin Henes, Jr. (Fellow), Milwaukee, Wis.,—1 book, "Milwaukee Proceedings of the Inter-State Postgraduate Medical Association of North America for 1931";

Dr. E. A. Baumgartner (Fellow), Clifton Springs, N. Y.—collected papers from the Clifton Springs Sanitarium and Clinic on "Studies in Tropical Sprue", bound in one volume;

Dr. David W. Kramer (Associate), Philadelphia, Pa.—4 reprints;

Dr. George B. Lake (Associate), Highland Park, Ill.—1 reprint;

Dr. C. Ray Lounsberry (Fellow), San Diego, Calif.—1 reprint;

Dr. V. C. Rowland (Fellow), Cleveland, Ohio—3 reprints;

Dr. A. Comingo Griffith (Fellow), Kansas City, Mo.—2 books formerly the property of his father, Dr. Jefferson D. Griffith: "A Compleat Treatise of the Gravel and Stone" by Nicholas Robinson, M.D., 1723;

"A Treatise on Surgical Anatomy" by Velpeau (in two volumes), 1830.

Dr. Samuel H. Snider (Fellow), Kansas City, Missouri, addressed the Hennepin County, Minnesota Medical Society on March 16 on "Routine Methods in the Diagnosis of Pulmonary Tuberculosis". He also addressed the Minnesota Trudeau Society that evening on the subject of "Bronchial Function in Pulmonary Tuberculosis".

Dr. Grafton Tyler Brown (Fellow), Washington, D. C., addressed the Atlantic County Medical Society, Atlantic City, N. J., on March 11. His subject was "Seasonal Hay-Fever", with special reference to the Middle Atlantic States. Dr. Samuel Barbash (Fellow) and Dr. Samuel L. Salasin (Fellow), both of Atlantic City, participated in the discussion.

Articles by Dr. Brown also appeared in the January, 1932, issue of the Journal of Allergy and in the February issue of Archives of Otolaryngology.

Dr. Harlow Brooks (Fellow), New York, N. Y., was elected President, and Dr. L. T. LeWald (Fellow), New York, N. Y., was elected Treasurer of the International Medical Club of America, at the Annual Meeting on April 1, 1932.

"Smilin' Thru" is the title of an attractive illustrated book recently published by the Hudson County Tuberculosis Hospital and Sanatorium, its staff and friends, "in recognition of the achievements and devotion to the welfare of society engendered by Dr. Berthold S. Pollak" (Fellow), on the occasion of the Twenty-fifth Anniversary of his medical directorship of that institution.

Dr. Warren Pearce (Fellow), Quincy, Ill., delivered the Chairman's address before the Medical Section of the Illinois State Medical Society meeting at Springfield, May 17-19, 1932.

Dr. Andrew C. Ivy (Fellow), Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, delivered the annual address before the Gorgas Medical Society of the School of Medicine, University of Alabama, May 7. His subject was "Physiologic Aspects of the Etiology, Symptoms, and Treatment of Gastroduodenal Ulcer".

Dr. Edward E. Cornwell (Fellow), Brooklyn, N. Y., read a paper before the American Therapeutic Society at Baltimore, May 17, on "A Problem of the Circulation".

Dr. David Riesman (Fellow), Philadelphia, Pa., delivered an address on "Vascular Crises" before the Evanston Branch of the Chicago Medical Society, April 7, 1932.

Dr. Arthur A. Shawkey (Fellow), Charleston, W. Va., addressed the Hempstead Academy of Medicine, Portsmouth, Ohio, on the evening of April 11, 1932. His subject was "The Hypertonic Infant".

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill., spoke before the Kankakee County Medical Society (Illinois), April 14, 1932, his subject being "Allergy of the Respiratory Tract".

Dr. Peter Whitman Rowland (Fellow), University, Miss., at a recent meeting of the State Medical Association (Jackson, Miss., April 12) announced his forty-ninth year of continuous membership in the Association.

Dr. Samuel A. Levine (Fellow), Boston, Mass., delivered an address and conducted clinics on various aspects of heart disease before the Orleans Parish Medical Society at New Orleans on March 31, 1932.

Dr. Edward J. Stieglitz (Fellow), Chicago, Ill., addressed the Saint Joseph Clinical Society (St. Joseph, Mo.) April 21, 1932, on "Nephritis in Pregnancy", and again, at a noon luncheon, on "The Etiology and Pathogenesis of Hypertension".

Dr. Robert L. Schaefer (Fellow), New York, N. Y., gave a talk before the Noon Day Study Club of Detroit on "Endocrine Diagnosis and Treatment", and spoke before the staff of Grace Hospital of Detroit on "The Anterior Lobe of the Pituitary", on April 15, 1932.

Dr. Udo J. Wile (Fellow), Ann Arbor, Mich., addressed the Fifty-ninth Annual Meeting of the Northern Tri-state Medical Association at Toledo, Ohio, on April 12, 1932. His subject was "The Fluid Status of Syphilis Therapy". Dr. Wile also gave a dermatological clinic.

Dr. Warren T. Vaughan (Fellow), Richmond, Va., spoke before the Association on "The Control of Pollen Allergy".

Dr. William C. Voorsanger (Fellow), San Francisco, Calif., was recently elected President of the California State Tuberculosis Association.

Dr. Arthur C. Christie (Fellow), Washington, D. C., President, Medical Society of the District of Columbia, has been selected as chairman of the executive committee in charge of the annual early diagnosis campaign of the Association for the Prevention of Tuberculosis, which was launched in the District the first part of April. In a talk, reviewing the history of "Tuberculosis Reporting", Dr. Christie appealed for more effective reporting of cases.

The annual session of the Medical Society of the District of Columbia was held, May 4-5, 1932, under the presidency of Dr. Christie.

Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y., delivered the Hermann M. Biggs Memorial Lecture at the New York Academy of Medicine on May 5, 1932. His subject was "Robert Koch and His Life Work." The Biggs lecture was established in 1925 by the widow of Dr. Biggs.

Dr. William D. Anderson (Fellow), Chattanooga, Tenn, was elected a vice president of the Tennessee State Medical Association at its annual meeting in Memphis on April 14, 1932.

Dr. Daniel J. Glomset (Fellow), Des Moines, Iowa, was made president-elect of Medical Society of the Missouri Valley at its annual meeting in Omaha, March 29-31, 1932.

Dr. Alfred Henry (Associate), Indianapolis, Ind., president, National Tuberculosis Association, addressed the Illinois Tuberculosis Association at its annual meeting in Danville, Ill., on April 25, 1932. He spoke on "Our Job Now".

Dr. John A. Lanford (Fellow), New Orleans, La., has been made chairman of a state cancer committee organized, February 22, by Dr. Sidney C. Barrow in cooperation with the American Society for the Control of Cancer.

Dr. Lewellys F. Barker (Fellow), Baltimore, Md., Professor Emeritus of Medicine, Johns Hopkins University School of Medicine, delivered the annual Alpha Omega Alpha lecture at Jefferson Medical College, Philadelphia, Pa., on March 4, 1932. His subject was "Medical and Other Conditions in Soviet Russia".

Dr. Louis Hamman (Fellow), Baltimore, Md., presided over the forty-ninth annual meeting of the American Climatological and Clinical Association, held at the Seaview Golf Club, Absecon, N. J., near Atlantic City, May 5-7. Among the speakers at the scientific sessions were the following Fellows: Dr. George R. Minot, Boston, Mass.; Dr. J. Burns Amberson, Jr., New York, N. Y.; Dr. Paul D. White, Boston, Mass.

Dr. Joseph H. Pratt (Fellow), Boston, Mass., was chairman of the roundtable discussion on diseases of the heart and Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y. was chairman of the roundtable discussion on diseases of the lungs.

At the Thirty-Third Annual Meeting of the American Therapeutic Society, held in Baltimore, Maryland, on May 16 and 17, the following officers were elected for the coming year:

President, Frank Smithies (Master), Chicago, Ill.;

1st Vice-President, Julius Friedenwald (Fellow), Baltimore, Md.;

2nd Vice-President, Alpheus F. Jennings (Fellow), Detroit, Mich.;

3rd Vice-President, Grafton Tyler Brown (Fellow), Washington, D. C.;

Secretary, Oscar B. Hunter (Fellow), Washington, D. C.;

Treasurer, Alphonse McMahon (Fellow), St. Louis, Mo.

Dr. Hugh S. Cumming (Fellow), Washington, D. C., early in March took the oath of office as Surgeon-General of the U. S. Public Health Service for the fourth time. Dr. Cumming entered the Service thirty-eight years ago and has been Surgeon-General since 1920.

The American Association of the History of Medicine held its annual meeting in Atlantic City, May 2, 1932, with Dr. David Riesman (Fellow), Philadelphia, presiding. The following Fellows contributed to the program: Dr. Carl V. Weller, Ann Arbor, Mich.; Dr. Charles W. Burr, Philadelphia, Pa.; Dr. William S. Middleton, Madison, Wis.; Dr. H. R. M. Landis, Philadelphia, Pa.; Dr. Lewellys F. Barker, Baltimore, Md.

Dr. Harold Swanberg (Fellow), Quincy, Ill., is the author of an article, "The X-Ray Diagnosis of Chronic Appendicitis", which appeared in the April, 1932, issue of the Quincy Medical Bulletin.

The Philadelphia Heart Association gave an intensive program on the diagnosis and treatment of heart disease in Philadelphia, May 16-19, inclusive. The following Philadelphia members of the College participated as shown:

Dr. Ross V. Patterson (Fellow), dean, Jefferson Medical College,—"A Rational Plan for the Diagnosis and Treatment of Heart Affections".

Dr. Edward J. G. Beardsley (Fellow), clinical professor of medicine, Jefferson Medical College,—"Problems Associated with Aortic Regurgitation".

Dr. Elmer H. Funk (Fellow), professor of materia medica, therapeutics, and clinical medicine, Jefferson Medical College,—"Acute Endocarditis".

Dr. Henry K. Mohler (Fellow), assistant professor of medicine, Jefferson Medical College,—"Heart Block".

Dr. Edward Weiss (Fellow), associate in medicine, Jefferson Medical College,—"Congenital Heart Disease".

Dr. William Egbert Robertson (Fellow), professor of theory and practice of medicine, Temple University Medical School,—"The Diagnosis of the Failing Heart Muscle".

Dr. H. Brooker Mills (Fellow), professor of pediatrics, Temple University Medical School, (and associates),—"Heart Disease in Children".

Dr. Joseph B. Wolffe (Associate), associate professor of cardiovascular diseases, Temple University Medical School,—"Coarctation of the Aorta" (with case demonstration).

Dr. E. B. Krumbhaar (Fellow), professor of pathology, U. of P. Medical School.—"Demonstration of the Pathology of the Cardiovascular System".

Dr. John Eiman (Fellow), pathologist, Presbyterian Hospital,—"Anatomy of the Conducting System with Demonstration of Injection of the Purkinje System and Demonstration of Injection of Coronary System".

Dr. William D. Stroud (Fellow), professor in cardiology, Graduate School of Medicine, U. of P.,—"Treatment of Cardiac Arrhythmia".

Dr. James E. Talley (Fellow), emeritus professor of cardiology, Graduate School

of Medicine, U. of P.,—"Cardiovascular Phenomena of Thyroid Disease".

Dr. S. Calvin Smith (Fellow), associate professor of cardiology, U. of P.,—"Demonstration and Discussion of Electrocardiography in Diagnosis and Treatment of Heart Disease".

Dr. Charles C. Wolferth (Fellow), Robinette Foundation, U. of P.,—"The Relation of Cardiology to General Medicine".

Dr. David Riesman (Fellow), professor of clinical medicine, U. of P. Medical School,—"Some of the Difficulties in the Diagnosis of Mitral Stenosis".

Dr. Truman Schnabel (Fellow), physician of the Philadelphia General Hospital and assistant in medicine, U. of P. Medical School,—"Diet and the Gastro-intestinal Tract in Relationship to Cardiovascular Disease".

Dr. William H. Kraemer (Fellow), Wilmington, Del., was elected president of the Alumni Association of Jefferson Medical College at the thirty-sixth annual meeting of the association, February 18.

The following Fellows were also elected to office:

Dr. Ross V. Patterson,—vice chairman;
Dr. Louis H. Clerf,—vice president;
Dr. Harold W. Jones,—treasurer.

Dr. Edward J. G. Beardsley (Fellow), Philadelphia, Pa., Governor for Eastern Pennsylvania, addressed the Bridgeport, Connecticut, Medical Association on "Practical Post-Graduate Instruction in our own offices", May 3, 1932.

Dr. Daniel P. Griffin (Fellow), Bridgeport, Conn., is President of the Association, and at his request Dr. Beardsley also spoke briefly on the objects and ideals of the American College of Physicians.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., recently read a paper before the Medical Society of New Jersey, at Atlantic City, on the subject "Recent Advances in the Treatment of Some Diseases in Children".

Dr. Pauline Williams (Fellow), Richmond, Va., national president of the Alpha Epsilon Iota Fraternity of medical women, presided at the biennial convention of that organization held at Portland, Ore., June 10-12, inclusive. This fraternity embraces a membership of 1,500 women physicians and women medical students; the chapters are established in twenty-two class A medical schools throughout the country.

Dr. Allen K. Krause (Fellow), Tucson, Ariz., delivered the Theodore B. Sachs resident lectures in tuberculosis at the University of Illinois College of Medicine, April 18-29. This lectureship is endowed by the Chicago Tuberculosis Institute.

Dr. John H. Peck (Fellow), Des Moines, Iowa, was re-elected President of the Iowa Tuberculosis Association at its recent annual meeting in Burlington.

Dr. J. A. Myers (Fellow), Minneapolis, Minn., addressed the Fifth Councilor District Medical Society at Boone, Iowa, April 13, on "Tuberculosis in Childhood".

The following Fellows of the College participated on the program at the sixty-fifth annual session of the Mississippi State Medical Association, April 12-14, at Jackson, Miss., as indicated:

Dr. Lloyd Thompon, Hot Springs, Ark,—"Modern Renaissance of Syphilis";

Dr. Allan C. Eustis, New Orleans, La.—"Headaches: Causes and Treatment";

Dr. James G. Carr, Chicago, Ill.—"Treatment of Cardiac and Renal Edema";

Dr. Edward C. Mitchell, Memphis, Tenn.—"Asthma from the Viewpoint of the Pediatrician";

Dr. Waller S. Leathers, Nashville, Tenn., presented the annual oration.

Dr. Henry A. Christian (Fellow), Boston, Mass., addressed the Mahoning County Medical Society, Youngstown, Ohio, on April 28, its sixth annual Postgraduate Day, on "Varieties of Bright's Disease and their Management" and "Diuretics and their Uses".

Dr. Samuel A. Levine (Fellow), Boston, Mass., also addressed the same meeting on "A Clinical Conception of Heart Disease"

and "Bedside Recognition and Treatment of Cardiac Irregularities".

Dr. Ernest R. Zemp (Fellow), Knoxville, Tenn., spoke on "Gastric Ulcer" before the ninety-ninth annual meeting of the Tennessee State Medical Association at Memphis, April 12-14.

At a meeting in the Embassy of Mexico, Washington, D. C., on April 5, Surgeon General Hugh S. Cumming (Fellow) was appointed President of a newly organized chapter of the Pan-American Medical Association for the District of Columbia.

Dr. Samuel A. Brown (Fellow), New York, N. Y., recently resigned as Dean of New York University and Bellevue Hospital Medical College, and has been made a member of the University Council. Dr. Brown had been Dean for sixteen years.

Dr. Henry J. Ullmann (Fellow), Santa Barbara, Calif., addressed the San Diego County Medical Society, May 5, on "The Work of the Cancer Commission".

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., was one of the guest speakers at the eighty-third annual session of the Medical Association of Georgia, May 17-20, at Savannah. Dr. Alvarez's subject was "Practical Points in the Care of Patients with Indigestion".

Dr. James H. Hutton (Associate), Chicago, Ill., has been appointed Consulting Endocrinologist to the hospitals of the Illinois State Department of Public Welfare.

The following Fellows of the College addressed the Medical and Chirurgical Faculty of Maryland at its recent meeting in Baltimore, April 26-27:

Dr. Henry A. Christian, Boston, Mass.—"Digitalis in Relation to the Therapy of Heart Disease";

Dr. Lay Martin, Baltimore, Md.—"Studies on a New Organic Material, Presumably an Enzyme, Secreted into the Gastric Juice";

Dr. Lewellys F. Barker, Baltimore, Md.—"Relation of the State Board of Health to the General Practitioner".

In connection with a special four months' course in Internal Medicine held at the Harvard University Medical School, April 1 to August 1, Dr. Frank Dennette Adams (Fellow), Boston, Mass., has charge, for six weeks, of a course in Internal Medicine at the Massachusetts General Hospital, which began June 20. During July, Dr. Samuel A. Levine (Fellow), Boston, Mass., will conduct a course in modern diagnosis and treatment of heart disease at the Peter Bent Brigham Hospital.

The following members of the College contributed to the program of the Nebraska State Medical Association, held at Lincoln, Nebr., May 24-26:

Dr. Ernest S. Wegner (Associate), Lincoln, Nebr.—"Infant Feeding";

Dr. Arthur D. Dunn (Fellow), Omaha, Nebr.—"Cholecystography";

Dr. Andrew C. Ivy (Fellow), Chicago, Ill.—"Physiology of Mucus Secretion with some experimental results on the prevention of Ulcer with 'Gastric Mucin'";

Dr. Walter C. Alvarez (Fellow), Rochester, Minn.—"Practical Points in the Handling of Patients with Gastro-Intestinal Disease".

Dr. Edgar B. Friedenwald (Fellow), Baltimore, Md., on May 13 addressed the Atlantic County Medical Society, Atlantic City, N. J., on "Diet Problems and Therapeusis in Children".

Dr. L. B. McBrayer (Fellow), Southern Pines, N. C., was re-elected Secretary of the Medical Society of the State of North Carolina at its annual meeting on April 20.

The following Fellows of the College delivered papers at the annual meeting of the National Tuberculosis Association held at Colorado Springs, June 6-9.

Dr. James Burns Amberson, Jr., New York, N. Y.—"Comparative Value of Paper and Celluloid Films for Chest Roentgenograms; Report of 1,000 Cases";

Dr. Carl H. Greene, Rochester, Minn.—

"Treatment of Addison's Disease with Cortical Hormone of the Suprarenal Gland".

Dr. Gerald B. Webb (Fellow), Colorado Springs, Colo., addressed the annual dinner meeting on "Robert Koch".

Dr. Roy Lyman Sexton (Associate), Washington, D. C., addressed the Tippecanoe County Medical Society, May 5, at Lafayette, Ind., on "Colon Disturbances and Involvements including Endocrine Aspects".

Dr. William S. Middleton (Fellow), Madison, Wis., and Dr. Arthur L. Anderson (Fellow), Springfield, Mo., addressed the Missouri State Medical Association at Jefferson City, May 23-26, on "Syphilis of the Circulatory System" and "Value of Routine Basal Metabolism in the Examination of Patients", respectively.

Dr. Louis E. Viko (Fellow) was recently appointed Health Officer of Salt Lake City.

Dr. George G. Ornstein (Fellow), New York, N. Y., spoke before the Cambria County Medical Society, Cresson, Pa., May 12, on "Diagnosis and Treatment of Pulmonary Tuberculosis".

Dr. Willis F. Manges (Fellow), Philadelphia, Pa., delivered an address on "Relation of Sinus Infection to Pulmonary Diseases" before the Eleventh Councilor District Medical Society, May 19.

"Collapse Therapy in the Treatment of Pulmonary Tuberculosis" was the subject of a paper delivered by Dr. Charles H. Marcy (Fellow), Pittsburgh, Pa., before the Erie County Medical Society, Erie, Pa., on May 3.

Dr. Joseph H. Barach (Fellow), Pittsburgh, Pa., addressed the Crawford County Medical Society, May 9, on "Focal Infection".

Dr. James H. Means (Fellow), Boston, Mass., was re-elected Secretary of the Association of American Physicians at its recent meeting.

At the annual meeting of the American Gastro-Enterological Association, May 2, Dr. Charles G. Lucas (Fellow), Louisville, Ky., was reelected Secretary.

Dr. Arthur L. Bloomfield (Fellow), San Francisco, Calif., was elected President of the American Society for Clinical Investigation, on May 2.

Dr. Howard T. Karsner (Fellow), Cleveland, Ohio, was recently reelected Secretary of the American Association of Pathologists and Bacteriologists for the ensuing year.

Dr. William E. Engelbach (Fellow), New York, N. Y., addressed the staff of St. John's Hospital, Brooklyn, May 3, on "Results of Therapy in Pituitary Disorders". On May 16, Dr. Engelbach addressed the joint meeting of the Baltimore Medical Society and the American Therapeutic Society at Baltimore on "Endocrine Therapy in Disorders of the Hypophysis".

Dr. Abraham M. Ornsteen (Fellow), Philadelphia, Pa., has been appointed Assistant Professor of Neurology in the University of Pennsylvania School of Medicine. Dr. Ornsteen has also been elected President of the Philadelphia Neurological Society.

Dr. John G. FitzGerald (Fellow), Toronto, Ont., has been appointed Dean of the University of Toronto Faculty of Medicine.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., as a guest speaker, addressed the Kiwanis Club of Woodbury, N. J., May 12, on "The Influence of the Hospital upon the Community".

Dr. Ralph K. Hollinshed (Fellow), Westville, N. J., was also a guest of the Club on this occasion.

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, was inducted as President of the American Society of Clinical Pathologists at its recent meeting in New Orleans.

Dr. David W. Kramer (Associate), Philadelphia, Pa., was recently appointed Visiting Physician to the Medical Staff at the St. Luke's and Children's Hospitals.

PERPETUAL MEMORIAL FUND
IN HONOR OF
DR. JOHN B. DEAVER

The Aid Association of the Philadelphia County Medical Society is establishing a special perpetual fund in honor of Dr. John B. Deaver, only the income of which will be used to afford aid to needy physicians and their families. All friends of Dr. Deaver are invited to participate. All money received will be placed in the Dr. John B. Deaver Perpetual Memorial Fund. Checks should be drawn to the order of the Aid Association of the Philadelphia County Medical Society and sent to:

Dr. Francis Heed Adler, Secretary,
313 So. 17th Street, Philadelphia, Pa.

OBITUARIES

DR. ORLANDO HENDERSON PETTY

Dr. Orlando Henderson Petty (Fellow), Philadelphia, Pennsylvania, an outstanding medical hero of the World War, died as the result of a self-inflicted gunshot wound, at his home on June 2, 1932. Dr. Petty was born in Cadix, Ohio, in 1874, and received his academic education in that State, with his B.S. degree from Franklin College. He was graduated in medicine from the Jefferson Medical College of Philadelphia in 1904. Dr. Petty served his internship at St. Timothy's Hospital, Roxborough, Philadelphia, in which institution he later became pathologist and visiting physician.

Shortly after Dr. Petty completed his internship, a latent lung lesion made itself evident and he was advised to live an open-air existence with restrictions as to physical activities. Following the enforced and unwelcome vacation, an opportunity presented itself to become associated with Dr. John B. Lowman, a distinguished surgeon of Johnstown, Pa., in the field of industrial surgery. After a year spent in this work Dr. Petty returned to the environs of Philadelphia, and soon built up a large general practice in Roxborough where he became intimately associated with that great physician and medical teacher, Milton H. Fussell. During this period Dr. Petty became actively engaged in clinical teaching at the Jefferson Medical College, in which unremunerative and disinterested labor he continued for many years.

Dr. Petty was, for a period, pathologist to the Germantown Hospital and faithfully served the City of Philadelphia as a medical inspector of its public schools.

At the time the United States entered the World War Dr. Petty, in spite of excellent reasons why he should delay his military service, applied for active service and was immediately assigned to the Marine Corps. He sailed for France in August, 1917, and was soon serving in the field with the Fifth Marines, Second Division. The Corps to which Dr. Petty was assigned was soon in the thick of battle and Dr. Petty distinguished himself by outstanding bravery and heroism. For his conduct on the field of battle and his efficient professional services, he received the Congressional Medal of Honor, The United States Distinguished Service Cross, the Croix de Guerre

of France with palm, and the War Cross of Italy. Dr. Petty shared with Dr. Joel T. Boone the signal honor of being the only two officers of the Medical Corps to receive the Congressional Medal of Honor.

Dr. Petty was severely gassed during his heroic work with the wounded and spent much time in the Military Hospital as a result. At the conclusion of the war Dr. Petty returned to his home city a nationally acknowledged hero, but in extremely poor physical and financial condition, to take up the problems of readjustment.

Without thought of self, Dr. Petty began immediately and with characteristic energy and enthusiasm his undergraduate teaching and, at the same time, expended strength, that his disordered body could ill afford, in many medical, military service and other civic undertakings. He was elected President of the Philadelphia County Medical Society, President of the Medical Club of Philadelphia, Commander of the Thomas Roberts Reath Post No. 186 of the American Legion, National Commander of the Army and Navy Legion of Valor, and was active and interested in many similar agencies.

In 1923, Dr. Petty, whose medical interests had been especially with the disorders of metabolism, was elected Professor of the Diseases of Metabolism in the Graduate School of Medicine of the University of Pennsylvania where he came in contact with many graduate physicians from various parts of the world. Medical articles and books from Dr. Petty's pen, and addresses by him, stimulated a new interest in disorders of nutrition. Dr. Petty built at the Philadelphia General Hospital a Department of Nutrition and headed an active service for the investigation of metabolic disorders.

For a short period in 1931 Dr. Petty served as Director of Public Health of Philadelphia to succeed the late Dr. Andrew A. Cairns, under whom Dr. Petty had worked many years as Medical School Inspector.

When one contemplates what Dr. Orlando Henderson Petty acomplished in the twenty-eight years that he lived after receiving his medical degree and considers the handicap of persistent ill health that had never been absent, one can but wonder at the spirit, the determination and the unconquerable ambition that drove him on. For many years prior to his military service, Dr. Petty's life was a continual struggle to overcome a more or less active tuberculous lesion which he would never, consciously acknowledge. Following the exposures and the physical and emotional stress of military life, the lung lesion became active and duodenal ulcer also developed which later was never entirely symptom free. During the last months of Dr. Petty's life a prostatic lesion developed that demanded surgical attention in spite of the existing serious contra-indications. As though all this were not enough for one pain-racked and harrassed brave man to endure, nature further restricted Dr. Petty's activities by a serious, painful and disabling attack of coronary occlusion. Under the best conditions a physician in Dr. Petty's precarious state of physical and mental health could only find a way out by taking a prolonged rest with entire freedom from physical and emotional stress and strain. Dr. Petty was living in a de-

pressing period of our national history and the weight of all his ills and anxieties proved too great a strain. Throughout the United States are physicians whom Dr. Petty has taught, with whom he has served, or with whom he has maintained friendly contacts. All these and many other admirers and friends will sincerely regret his passing. Dr. Petty was a sincere, dogmatic, and conscientious teacher; perhaps, even in his end, there is a potential lesson for each of us to remember. A physician's health is his greatest asset and this, in spite of everything, he must preserve by a judicious care for his own body.

E. J. G. Beardsley, M.D., F.A.C.P., Governor for Eastern Pennsylvania).

DR. JOHN ALDEN LICHTY

Dr. John Alden Lichty was born in 1866. He received the degrees of Ph.B., Ph.M., and Ph.D. from Mount Union College, and M.D. from the University of Pennsylvania School of Medicine in 1893. He also did postgraduate work at the University of Pennsylvania in pathology and diseases of the digestive system; also postgraduate work at the University of Berlin. He was associate professor of medicine, University of Pittsburgh School of Medicine, from 1909 to 1923; visiting physician, Mercy Hospital, Pittsburgh, 1912 to 1923; visiting physician, Columbia Hospital, Pittsburgh, 1906 to 1923; consulting physician, Presbyterian Hospital, Pittsburgh, 1916; superintendent, Clifton Springs Sanitarium and Clinic, 1923 to the time of his death. He was a member and ex-president, Ontario County Medical Society; member and ex-chairman of Medical Section, New York State Medical Society; member and ex-vice chairman of Medical Section, American Medical Association; ex-member and ex-chairman of Medical Section, Pennsylvania State Medical Society; member and ex-president, American Gastro-Enterological Association; member American Climatological and Clinical Association, and member American Association for Advancement of Science. Dr. Lichty was also a member of the Alpha Tau Omega and Phi Beta Pi fraternities. Dr. Lichty was the author of many articles published in various medical journals and was the author of the chapter on Arthritis of the Text, "Diseases of Middle Life", F. A. Davis Company, also of the chapter on Appendicitis of Tice's "Practice of Medicine".

Dr. Lichty was elected a Fellow of the American College of Physicians on December 29, 1916, and, therefore, was one of the earliest members of the organization. He served in a great many capacities in the College, including, member of the Board of Regents, 1922 to 1930; Third Vice-President, 1930 to 1932. One of his greatest contributions to the College was the early organization and Chairmanship of the Credentials Committee, on which he served faithfully and painstakingly for several years. The College was very near to Dr. Lichty and even after the onset of his last illness he tried to serve the College and to attend one of its annual meetings.

DR. CHARLES ROLLIN GRANDY

Charles Rollin Grandy (Associate), Norfolk, Va., died, June 10, 1932, from a cerebral hemorrhage and heart disease; aged 61 years.

Dr. Grandy was born in Norfolk, educated at the Norfolk Academy and the Bellevue High School. He held the degrees of A.B. and M.D. from the University of Virginia, the latter having been conferred in 1892. He did post-graduate work at the University of Berlin and the University of Freiburg, Germany. He was formerly attending physician to the Norfolk Protestant Hospital and physician-in-charge of the Norfolk Tuberculosis Clinic. For many years, he was chairman of the Norfolk School Board.

Early in Dr. Grandy's career, he became interested in combating tuberculosis, to which work he devoted his energy the greater part of his life. He was responsible for the first comprehensive public health law in the State of Virginia. He organized the Anti-Tuberculosis League of Norfolk, and was its first president. He served in this capacity for twenty-seven years. In recognition of his service, Norfolk dedicated its tuberculosis sanatorium last November as the Charles R. Grandy Sanatorium.

Dr. Grandy was an ex-president of the Norfolk County Medical Society, a member of the Seaboard Medical Association, an ex-president of the Medical Society of Virginia, a Fellow of the American Medical Association, a member of the American Association for the Advancement of Science, a member of the American Public Health Association, a member of the National Tuberculosis Association, and had been an Associate of the American College of Physicians almost from its inception.

DR. NELSON GAPEN

Dr. Nelson Gapen (Fellow), Washington, D. C., died January 7, 1932, of mastoiditis and meningitis; aged, 53 years.

Dr. Gapen was born in Washington, where he attended public school and graduated from the Georgetown University School of Medicine in 1900. He served his internship in the Garfield Memorial Hospital of Washington, and pursued various post-graduate courses thereafter at the Army Medical School, Harvard Medical School, and the University of Michigan Medical School. For a time, he was Director of the Mary Imogene Bassett Hospital, of Cooperstown, New York. During the World War, he was in the office of the Chief Surgeon, Air Service, U. S. A., assisted in the formation of the original Medical Research Board for Aviation, and attained the rank of Colonel. At the time of his death he was Professor of Materia Medica, Pharmacology and Therapeutics in the Georgetown University School of Medicine. Dr. Gapen was a member of the Medical Society of the District of Columbia, the Association of Military Surgeons, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929.

(Furnished through the courtesy of EUGENE R. WHITMORE, M.D., F.A. C. P., Washington, D. C.)

DR. GEORGE HENRY SHERMAN

Dr. George Henry Sherman (Associate), Detroit, Michigan, died April 19, 1932, following an operation for appendicitis, in a hospital at Melbourne, Fla., aged 74 years.

Dr. Sherman was a graduate of the Chicago Medical College, 1883; he had not been in practice for several years.

DR. ALEXANDER BROWN KALBAUGH

Dr. Alexander Brown Kalbaugh (Associate), Westernport, Maryland, died suddenly May 15, 1932, of coronary embolism, aged 48 years.

Dr. Kalbaugh was a graduate of the University College of Medicine, Richmond, Va., 1907; he did postgraduate work at the University of Liverpool during 1919. During the World War he served as First Lieutenant in the Medical Corps of the Air Service at Le Bourget and Orley Air Fields, France; he also served with Charge de Assault, French Tank Corps.

Dr. Kalbaugh was an ex-president of the Allegany-Garrett County Medical Society, an ex-vice president of the Tri-State Medical Society, member of the Medical and Chirurgical Faculty of Maryland, member of the Southern Medical Association, a Fellow of the American Medical Association and had been an Associate of the American College of Physicians since 1921.

DR. ARTHUR J. BURRIDGE

Dr. Arthur J. Burridge (Fellow), Winnipeg, Manitoba, Canada, died March 15, 1932, aged 56 years.

Dr. Burridge was born in London, Ontario, Canada; attended the public and high schools of Winnipeg, and the Manitoba Medical College, from which he graduated in 1897. For many years he was Internist to the Grace Maternity Hospital and a member of the honorary attending staff of the Winnipeg General Hospital; he was Associate Professor of Medicine on the University of Manitoba Faculty of Medicine.

Dr. Burridge was a member of the Winnipeg Medical Society, the Manitoba Medical Association, and had been a Fellow of the American College of Physicians since January 30, 1920.